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[Intervention Review]

Interventions for helping people recognise early signs of recurrence in bipolar disorder

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ABSTRACT

Background

Recurrence rates for bipolar disorder are high despite effective treatments with mood stabiliser drugs. Self-help treatments and psychological treatments that teach patients to recognise and manage early warning symptoms and signs (EWS) of impending manic or depressive episodes are popular with patients. The main aim of such interventions is to intervene early and prevent bipolar episodes, thereby increasing the time to the next recurrence and preventing hospitalisation.

Objectives

To compare the effectiveness of an EWS intervention plus treatment as usual (TAU) versus TAU (involving and not involving a psychological therapy) on time to manic, depressive and all bipolar episodes (the primary outcome), hospitalisation, functioning, depressive and manic symptoms.

Search methods

Relevant studies identified by searching Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References - searched on 20/10/2005), supplemented with hand searching the journal Bipolar Disorders, searching the UK National Research Register, checking reference lists of included studies and contacting authors.

Selection criteria

Only randomised controlled trials (RCTs) were included. Participants were adults with a diagnosis of bipolar disorder based on standardised psychiatric criteria.

Data collection and analysis

Two reviewers independently rated trials for inclusion. Data were extracted from included trials by reviewers using a data extraction sheet. Authors of all the included studies were contacted for any additional information required. Time to recurrence data was summarised as log hazard ratios, dichotomous data as relative risk and continuous data as weighted mean difference, using random effects models to calculate effect size only when there was heterogeneity in the data.

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Main results

Eleven RCTs were identified, but only six provided primary outcome data. All six RCTs were of high quality. Time to first recurrence of any type (RE, hazards ratio 0.57, 95% CI 0.39 to 0.82), time to manic/hypomanic episode, time to depressive episode, and percentage of people hospitalised and functioning favoured the intervention group. Neither depressive nor hypomanic symptoms differed between intervention and control groups.

Authors' conclusions

This review shows a beneficial effect of EWS in time to recurrence, percentage of people hospitalised and functioning in people with bipolar disorder. However, the absence of data on the primary outcome measure in so many included studies is a source of concern and a potential source of bias. Mental health services should consider routinely providing EWS interventions to adults with bipolar disorder, as they appear to reduce hospitalisation and therefore may be cost-effective.

PLAIN LANGUAGE SUMMARY

Interventions for helping people recognise early signs of recurrence in bipolar disorder

Bipolar disorder (BPD), or manic-depressive psychosis, is a common and severe mental illness, with a lifetime prevalence of 1-2%. BPD is characterised by two types of recurrence, mania and depression. High rates of recurrence and associated adverse consequences occur in spite of a range of effective treatments. Early warning signs (EWS) interventions, targeted at improving the recognition and self-management of manic and depressive symptoms, are intended to train people with recurrent bipolar affective disorder to recognise early warning signs of recurrence and to avert adverse outcomes. This review demonstrated that these interventions, in addition to treatment as usual (TAU), including medication and regular appointments with health professionals, have benefits on time to recurrence and hospitalisation. Compared with TAU only, EWS interventions also resulted in improved functioning at eighteen months, although these data were sparse and the findings should be interpreted with caution. EWS interventions did not appear to have any effect on depressive or manic symptoms, although again, these findings were based on small numbers of potentially selected patients in remission. It should be noted that EWS was used along with other psychological interventions, and it is not entirely clear what proportion of the beneficial effect was due to the EWS intervention alone.

BACKGROUND

Bipolar disorder (BPD), or manic-depressive psychosis, is a common and severe mental illness with a lifetime prevalence of one to two per cent (Robins 1984; ten Have 2002). BPD is characterised by two types of recurrence, mania and depression. Mania is characterised by periods of elation or irritable mood lasting at least four days, coupled with other symptoms of overactivity, reduced need for sleep, disinhibition, increased self-esteem or grandiosity and increased talkativeness (APA 1995). Depression is characterised by core symptoms of depressed mood and loss of interest for at least two weeks, coupled with other symptoms such as changes in sleep pattern, appetite and concentration, low self-esteem, hopelessness, self-blame and suicidal ideation. Psychotic symptoms such as delusions and hallucinations are seen in a substantial proportion of patients in either the manic or depressed phases of the disorder. Recurrence rates are high, at around 50 per cent at one year, and 70 per cent at four years (Coryell 1989; Harrow 1990; Tohen 1990; O'Connell 1991; Keller 1992; Gitlin 1995) after a manic episode, in modern naturalistic studies. BPD patients were found to be symptomatic with recurrence or inter-episode symptoms of mania or depression for 47 per cent over a mean follow up of 13 years (Judd 2002). Recurrence and inter-episode symptoms impair function, marital relationships, employment and quality of life (Gitlin 1995; Ozer 2002; Judd 2002). There is a high lifetime prevalence of attempted suicide rate, completed suicide, and also risks to others through violence, neglect of dependents or reckless behaviour (Goodwin 1990; Morriss 2002).

High rates of recurrence and their adverse consequences occur in spite of a range of effective treatments such as mood stabilisers (Bowden 2000; Burgess 2003). Surveys of patient organisations in UK and US reveal a strong wish by patients for both self-help and psychological treatments in addition to pharmacotherapy (Lish 1994; Hill 1996). Self-help treatments may empower patients and

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enable them to take more control over their care and life decisions.

One form of self-help treatment and psychological intervention is to teach BPD patients to recognise early signs of the recurrence of mania and depression (Perry 1995; Perry 1999). This type of secondary prevention is widely used in medicine e.g. to promote early treatment of hypoglycaemia in diabetes mellitus or myocardial infarction. The approach has been practiced for many years in BPD patients (Jacobson 1965). Three retrospective studies (Molnar 1988; Smith 1992; Lam 1997) and two prospective studies (Altman 1992; Keller 1992) showed identifiable and consistent early or "prodromal" symptoms of manic or depressive recurrence at two to four weeks before full recurrence in most patients with BPD. These prodromal symptoms are idiosyncratic to both the individual and type of recurrence (mania or depression). They may be more consistent and easier to recognise for mania than depression (Molnar 1988 , Smith 1992). The definition of prodromal symptoms that represent the focus of the present review is early warning signs (EWS) of impending recurrence for persons already diagnosed with bipolar disorder. These prodromal symptoms are distinct in definition from those prodromal changes that precede the initial onset of major mental disorder (Bustillo 1995).

Individuals who cope well with the prodromal symptoms of mania and depression are less likely to be hospitalised (Joyce 1985) and show improved social and occupational function (Lam 1997). Cognitive behaviour therapy targeted at improving the recognition and self-management of manic and depressive prodromes has been reported as effective in delaying both depressive and manic recurrence (Lam 2000; Lam 2003). Recognition of EWS may also avert adverse outcomes. For instance, in the event of an episode, plans can be made for child care so that children are not neglected, for financial control to prevent reckless spending, and avoidance of previous circumstances that in the past have led to violence or re-offending.

Adverse outcomes from self-monitoring of early recurrences of BPD have been reported, with interventions involving the identification and management of EWS (Morriss 2004). Patients may become over-confident that they can use these techniques to prevent recurrence, and stop their mood-stabilising medication prematurely. Individuals in the prodrome of depression may ruminate on their depression with a further worsening of their depressive symptoms. False alarms may occur, and people may seek more hospital care or receive higher doses of medication such as antidepressants without any obvious benefit (Perry 1999).

Recent work has indicated that the effectiveness of CBT in bipolar disorder on time to any recurrence and symptoms of depression and mania was confined to patients without numerous previous bipolar episodes (Scott 2006). A large number of previous bipolar episodes has been associated with neuropsychological impairment (Denicoff 1999) and poor handling of stress (Hammen 1997). However, age, gender and baseline medication did not influence the effectiveness of the EWS intervention (Perry 1999). Thus, it is predicted that the effectiveness of interventions for EWS might vary according to number of previous bipolar episodes.

At present, the precise mechanism of action of EWS interventions in delaying recurrence in BPD remains unclear. EWS interventions appear effective in BPD patients who show good or poor adherence to medication (Colom 2003b; Colom 2003c). Time spent with a therapist does not explain the effectiveness of EWS interventions (Colom 2003b; Colom 2003c). EWS interventions may be effective because milder symptoms in the early stage of recurrence are easier to treat than more severe symptoms later in the recurrence. Patients report feeling more confident about returning to work and taking on other responsibilities in their lives, because EWS interventions forewarn the patient of a recurrence in time for the BPD patient to prevent any serious harm to their lives (Perry 1999; Morriss 2004).

Previous research has indicated that family members detect early warning signs later than the person diagnosed with schizophrenia (Birchwood 1989). Given this finding and other research indicating that some EWS in bipolar disorder are likely to be subjectively perceived (for example, changes in perception of colours and noise), EWS interventions should be more effective when the person with bipolar disorder is trained to recognise early signs rather than the carer. However, inclusion of family members in training might enhance the outcome of EWS interventions because they may recognise additional EWS signs due to behaviour (for example playing particular pieces of music), can be a point of reference if the patient wants to discuss the significance of an EWS, and can provide both practical help and emotional support.

There is encouraging evidence of the potential benefits of relapse prevention in serious mental illness (Mueser 2002). There is no systematic review of the clinical effectiveness of the range of self-help, medication, psycho-education and psychotherapy (principally cognitive behaviour therapy and family therapy) approaches that incorporate the recognition and prompt management of early or prodromal symptoms of recurrence. The primary target of such interventions is to increase time to the next recurrence and reduce recurrence, but there may be additional benefits in terms of improving social and occupational function, quality of life, depressive symptoms and patient empowerment. There is some evidence to suggest that persons with minimal training are able to teach these skills (see Perry 1999). One implication might be that people who use services could train other service users in these potentially efficacious techniques, thus making the intervention more widely available. This review seeks to examine whether participation of caregivers in training influences the effectiveness of the intervention. The review also aims to investigate whether outcomes differ significantly if EWS represents the primary focus of the intervention or is only one of a number of techniques taught.

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OBJECTIVES

The overall aim was to conduct a systematic review of all intervention studies that included systematically teaching the recognition of early warning signs (EWS) of recurrence to people diagnosed with bipolar disorder and/or their carers. The objectives were:

1. To compare the effectiveness of an EWS intervention plus treatment as usual (TAU) versus TAU not involving a psychological therapy on time to manic, depressive and all bipolar episodes.

2. To compare the effectiveness of an EWS intervention plus TAU versus TAU plus another psychological therapy on time to manic, depressive and all bipolar episodes.

3. To compare the effectiveness of intermittent medication used on recognition of EWS without continued mood stabilising medication versus TAU involving continued mood stabilising medication on time to manic, depressive and all bipolar episodes.

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Only randomised controlled trials were included. Studies were not excluded on the basis of language, country of origin or publication status.

Exclusion criteria

Studies that were not randomised controlled trials were excluded. These included case series, pre and post-intervention studies and those studies with a non-random allocation from waiting list.

Types of participants

Inclusion criteria

Adults with a diagnosis of bipolar disorder or associated diagnoses based on standardised psychiatric criteria (including Research Diagnostic Criteria, DSM IV, ICD-10). Adults were included at any stage of the disorder and in any treatment setting.

Exclusion criteria

The review excluded studies of participants where:

1. The primary diagnosis was another disorder (for example, panic, eating disorders)
2. Participants were selected on the basis of a non-psychiatric medical condition (for example, cancer, human immune deficiency syndrome)
3. People aged sixteen or under
4. People living exclusively in institutions e.g. nursing home, prisons but not excluding temporary care arrangements such as hospitalisation
5. 'At risk' populations who have not yet received a definite diagnosis of bipolar disorder.

Types of interventions

Inclusion criteria

Interventions designed to systematically train people with a diagnosis of bipolar disorder to recognise early warning signs of recurrence of episodes were included. Each person in the study must have received at least one hour of training specifically in recognising and managing EWS. EWS interventions require detailed history taking, with or without additional techniques such as diary keeping and card sorting techniques, and a plan of action based on the EWS. Therefore, EWS interventions required at least one hour of face to face clinical contact. Any intervention that included EWS interventions either as a major focus or as one component of an intervention package was included. The interventions might be individually based or group based. The interventions to be included would also encompass self-help approaches. Studies involving family members or carers were also included. EWS interventions were be included if they were carried out in community, primary care or secondary care settings.

During abstract review, in the absence of an explicit description of early warning signs training, studies where the intervention was described as cognitive, family, psychosocial, education, self-monitoring, interpersonal, relapse prevention, self-help, problem-solving, counselling or targeted/intermittent medication were considered as potentially including EWS interventions.

The following comparisons were to be made:

1. To compare the effectiveness of an EWS intervention plus treatment as usual (TAU) versus TAU not involving a psychological therapy on time to manic, depressive and all bipolar episodes
2. To compare the effectiveness of an EWS intervention plus TAU versus TAU plus another psychological therapy on time to manic, depressive and all bipolar episodes
3. To compare the effectiveness of intermittent medication used on recognition of EWS without continued mood stabilising medication versus TAU involving continued mood stabilising medication on time to manic, depressive and all bipolar episodes.

Exclusion criteria

Studies where both groups simultaneously received the same psychological intervention involving EWS were excluded (for example, psychological therapy versus psychological therapy in addition to medication).

Types of outcome measures

Primary outcome

1. Time to first recurrence of any type.

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Secondary outcomes

1. Manic, hypomanic or mixed affective episodes and time to depressive episodes.

2. Percentage of people who were hospitalised.

3. Measures of symptoms, functioning and medication, where available at 3,6, 12, 18 and 24 months or more after baseline:

Functioning: Social functioning/interpersonal functioning, occupational functioning (e.g. MRC Social Performance Scale (Hurry 1983).

Symptoms: Continuous measures of symptoms (depression on Beck Depression Inventory; BDI (Beck 1961); Hamilton Depression Rating Scale; HDRS (Hamilton 1960); Montgomery-Asberg Depression Rating Scale; MADRS (Montgomery 1979); Hospital Anxiety and Depression Scale; HAD (Zigmond 1983); mania on Bech Rafaelsen Mania Scale (Bech 1978); Young Mania Scale (Young 1978); Longitudinal Interval Follow-up Evaluation; LIFE (Keller 1987); Internal States Scale (Bauer 1991); Altman Mania Scale (Altman 1997).

Medication: mg equivalents of chlorpromazine, imipramine, diazepam, lithium, valproate, carbamazepine.

4. As a measure of acceptance of the intervention, satisfaction with treatment approach.

We also considered other outcomes that might be particularly important to consumers such as quality of life (EuroQol Group 1990) and perceived control over illness (Lam 1997).

Search methods for identification of studies

1. Electronic bibliographic databases

Electronic searches were undertaken using Cochrane Collaboration Depression, Anxiety and Neurosis controlled trials registers (CCDANCTR-Studies and CCDANCTR-Studies).

Electronic search terms were:

CCDANCTR-Studies - searched on 20/10/2005

Diagnosis = “Affective Disorder” or “Affective Psychosis, Bipolar” or “Bipolar Depression” or “Bipolar I Disorder” or “Bipolar II Disorder” or “Cyclothymic Disorder” or “Depression, Psychotic” or “Depression, Recurrent” or “Excited Psychosis” or “Major Affective Disorders” or “Mania” or “Manic Disorder” or “Bipolar Affective Disorder” or “Bipolar Not Otherwise Specified” or “Schizoaffective Disorder” or “Psychoses” or “Psychotic Disorders”.

and

Intervention= “Clinical Status” or “Cognitive Behavioral Therapy” or “Cognitive Therapy” or “Consumer Advocacy” or “Consumer Led Care” or “Early Intervention” or “Education” or “Family-Focused Psychoeducational Therapy” or “Family Therapy” or “Group Therapy” or “Inpatient Family Intervention” or “Marital Therapy” or “Monitoring” or “Self-Directed Health and Social Care Use” or “Psycho education or ”Psychotherapy“ or ”Self-Evaluation“ or ”Self Monitoring“ or ”Skills Training“ or ”Spouses“.

CCDANCTR-References - searched on 20/10/2005

Keyword = Bipolar* or Mania or Manic* or Cyclothymic

and

Free-Text = ”Clinical Status“ or ”Cognitive Behavioral Therapy“ or ”Cognitive Therapy“ or ”Consumer Advocacy“ or ”Consumer Led Care“ or ”Early Intervention“ or Education or ”Family-Focused Psychoeducational Therapy“ or ”Family Therapy“ or ”Group Therapy“ or ”Inpatient Family Intervention“ or ”Marital Therapy“ or ”Monitoring“ or ”Self-Directed Health and Social Care Use“ or ”Psychoeducation“ or ”Psychotherapy“ or ”Self-Evaluation“ or ”Self Monitoring“ or ”Skills Training “ or ”Spouses“ or ”relapse prevention“ or ”early warning“

2. Handsearches

A hand search of all issues of Bipolar Disorders was carried out

3. NHS National Research Register (NRR)

This was inspected for information regarding ongoing research trials.

4. Reference Lists

All reference lists of selected studies and relevant reviews were inspected for additional relevant titles

5. Personal communication

We contacted researchers who have previously published in this area

Data collection and analysis

1. Decision to include or exclude study from review

Inspection of citations

All abstracts were independently reviewed by two out of three review authors (MAF, RM) with reference to the inclusion/exclusion criteria, and a decision was made whether to retrieve the full report of the study. The number of abstracts identified, accepted and rejected was recorded.

Inspection of retrieved reports

Once the full reports were retrieved, they were inspected for relevance to the review and inclusion and exclusion criteria applied. Studies not meeting the predetermined criteria were excluded. A record was made of the number of papers retrieved, the number of papers excluded and the reasons for exclusion.

2. Data extraction

A formal data extraction form was designed. Information regarding methods, participants, comparison groups, interventions and outcomes (noting where primary and secondary outcomes were not measured, or measured but not reported) was tabulated. Data were recorded to assess potential sources of clinical heterogeneity, including study design, participant characteristics and aspects of intervention content and delivery. All included studies were rated according to methodological quality criteria (see following section). Data extraction was performed by MF and JMcC, except for time to recurrence data, which were extracted by AJ and PW.

Determining whether described intervention included training in recognising and managing EWS

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The essential elements of early warning signs (EWS) monitoring were defined as:
1. Education to increase awareness of EWS and identification of these EWS
2. Person with bipolar disorder learning to self-monitor for EWS (e.g. mood monitoring), or carers and/or health professionals learning to monitor on behalf of the person with bipolar disorder
3. Early action to prevent development of recurrence (e.g. early help seeking or self-coping methods).
Where the information was ambiguous in the original report, attempts were made to contact the corresponding author of the study, or the first or most senior author when the corresponding author was not designated. A standard letter was sent by post or e-mail requesting the authors to clarify whether the intervention included early warning signs training, and if yes, whether the intervention was systematically employed with all participants. A further letter was mailed if the author did not respond to the initial letter. If there was no response to the second mailing, the study was then excluded from any further analysis.

All studies were categorised by:

- Target of intervention: 1. Interventions targeted at patient's own recognition of early warning symptoms; 2. Interventions targeted at recognition of early warning symptoms by carers or health professionals; 3. Interventions targeted at both patient and carer
- Individual or group treatment
- Focus of intervention: EWS was primary focus of intervention or one component of a multifaceted intervention
- Intervention as an addition or replacement for treatment as usual (TAU): 1. Intervention targeting early warning symptoms plus TAU versus TAU not including psychological treatment; 2. EWS intervention plus TAU versus another psychological treatment not involving EWS plus TAU; 3. EWS intervention with intermittent medication use in presence of EWS without continued mood stabiliser medication versus TAU using continued mood stabiliser medication
- EWS intervention involved only help-seeking from others, or EWS intervention involved other self-directed coping
- RCT involved euthymic BPD patients or BPD patients who were in depressive episode
- RCT included BPD patients with axis 1 or axis 2 psychiatric comorbidity (APA 1995) or excluded patients with axis 1 or 2 comorbidity.

3. Assessing methodological quality of studies

All RCTs were assessed for methodological quality. The items assessed were allocation concealment, method of randomisation, blinding, whether an intention to treat analysis was used and attrition. Allocation concealment and the method of randomisation were rated as either clear, unclear or inadequate. When the analysis reported was not an intention to treat analysis, we contacted the authors to try to obtain the results from the intention to treat analysis. Loss to follow-up was rated as either adequate (80 per cent or more follow-up) or inadequate (less than 80 per cent follow-up). Blinding was reported as either single, double or open, and where possible, we reported who was blinded in the trial. It was not possible to explore each of these methodological factors in a meta-regression as planned in the protocol, due to the sparsity of information available in the trials. Missing data were not imputed according to a best/worse case scenario, because the primary outcome was time to event data rather than categorical data.

4. Methods of statistical analysis

Treatment outcomes

The treatment outcomes relevant to this study were measured as time to recurrence of episodes, measures of symptoms and outcomes presented as dichotomous (hospitalisation/no hospitalisation) or continuous (means and standard deviations on rating scales).

Choice of methods for pooling of data

Dichotomous data were summarised in terms of relative risks. Time to recurrence data were summarised in terms of log hazard ratios. Log hazard ratios and the standard errors of the log hazard ratios were entered into Review Manager software, and analysed using the generic inverse variance method. These data were extracted from the published papers using the methods described by Parmar (Parmar 1998). Continuous data such as medication, symptomatology and functioning measured with standardised, published measures were summarised in terms of a difference in means, provided skewness was not too great. Continuous data were classed as being skewed if the standard deviation was over half the size of the mean (this is only true if the data can take positive values only, it does not apply to change data, for example). Skewed data were not pooled, and the results were presented in additional tables, with no statistical analyses performed on these data. Where this was the case, we contacted the study authors to obtain the change from baseline data that could be included in the analyses. Where data had been reported at a number of different time points throughout the course of a study, we reported when data had been measured within the trial, what had been reported within the published paper, and combined the data at clinically relevant intervals. Methods for the meta-analysis of continuous aggregate longitudinal data have been described (Jones 2005), and the method that was applied to the data in this review were analysis at independent time points, thus ignoring the correlation between the time points within an individual study.

Meta-analysis

We aimed to conduct three types of meta-analysis:

- Intervention targeted at recognition of EWS plus TAU versus TAU not involving psychological treatment
- Intervention targeted at recognition of EWS plus TAU versus another psychological control therapy plus TAU
- Intervention targeted at recognition of EWS coupled with intermittent medication use without continued mood stabilising medication versus TAU using continued mood stabilising

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medication.

Once the results of each study were summarised using an effects measure, an average value of the effect was computed across studies using either a 'fixed effect' model, if there was little heterogeneity, or a 'random effects' model when there was unexplained heterogeneity.

Heterogeneity

If clinical heterogeneity was too great, or methodological quality too poor, studies were not pooled in a meta-analysis. A chi-squared test for heterogeneity was undertaken, and the I-squared statistic was calculated. If statistical heterogeneity was indicated ($p<0.1$), then attempts were made to further investigate potentially influential study characteristics via meta-regression. Random effects modelling was employed where significant residual heterogeneity existed. A distinction was made between quantitative and qualitative heterogeneity.

It was acknowledged that certain subgroup analyses might not be possible due to limited number of studies or insufficient information available. Where this occurred, a qualitative review of information was completed if possible. The following subgroup analyses were planned:

- depressed episode (presence or absence) at baseline
- axis 1 or axis 2 comorbidity (presence or absence) at baseline
- EWS as primary focus of the intervention or as part of another intervention
- EWS intervention delivered to patient only or patient and carer or health professional
- EWS intervention delivered to carer only versus carer and patient
- EWS intervention delivered individually versus group intervention
- EWS intervention promotes only help seeking from others versus additional self-directed coping.

Publication bias

Publication bias was assessed by visual inspection of funnel plots. Consideration was given to within-study selective reporting bias (Hahn 2000; Williamson 2005).

RESULTS

Description of studies

Electronic searches of the CCDAN Controlled Trials Register were conducted to identify relevant studies. Thirty-five studies were relevant, based on the abstracts. These papers were obtained and scrutinised by two review authors (RM and MF). Eight of these met our inclusion criteria. Hand searching of the Bipolar Disorders journal revealed four relevant abstracts, of which only one met our inclusion criteria when the full paper was obtained (Meyer 2003, included under Ongoing studies). None were included from the reference list of other included studies. Two other papers were included after reviewing the original paper when they were published (Lam 2005; Scott 2006). In total, eleven studies met our inclusion criteria. One of the studies was reported twice (Lam 2003; Lam 2005) and another was reported three times (Simoneau 1999; Miklowitz 2000; Miklowitz 2003). One was an ongoing study (Meyer 2003). There is an additional ongoing study that is likely to be relevant to the review, but at present we do not have data (Ball 2003).

1. Excluded studies

Please refer to Table of Excluded Studies for details of individual trials.

2. Ongoing trials

One study (Meyer 2003) was presented as a conference proceeding, and the author supplied us with the first three months follow-up results. The author was contacted for further results, but we did not receive any further data. We have contacted the author of another study which has published its methodology (Ball 2003), but we have not received any data from that study.

3. Included studies

Three studies were duplicate reports (Lam 2003; Simoneau 1999 , Miklowitz 2000) and 11 studies (of which one was ongoing) met our inclusion criteria. The studies are described in the Table of Included Studies.

3.1 Methods

All trials were RCTs, but none were able to use a double blind technique due to difficulties in blinding psychosocial interventions. All studies tried to reduce bias by using independent outcome assessors, except three trials where blinding of the assessors was not mentioned (Van Gent 1991; Scott 2001; Meyer 2003) . The duration of follow-up ranged from 12 months to 24 months, except one trial where participants were followed up for only six months (Van Gent 1991).

3.2 Participants

All trials included people with a diagnosis of bipolar disorder, aged >18 years. All employed operational criteria for diagnosis (DSM-111-R, DSM-IV). Most of the trials used structured assessment (SCID, SADS) to arrive at the diagnosis, except two trials which used the opinion of senior psychiatrists (Colom 2003c; Colom 2003b), one study did not specify anything (Lam 2000), and another trial used the opinion of two independent psychiatrists (Van Gent 1991). Axis 1 and axis 2 psychiatric comorbidity were included in eight of the trials (Colom 2003c; Colom 2003c(a); Lam 2003;Meyer 2003; Perry 1999; Scott 2001; Scott 2006; Simon 2004). Other trials excluded axis 1 and axis 2 psychiatric morbidity or did not state whether these morbidities were included or excluded.

3.3 Interventions

In all studies, treatment as usual (TAU) included treatment with medication and outpatient appointments with a psychiatrist. In

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two trials (Colom 2003c; Colom 2003b), TAU was supplemented by 20 sessions of non-structured group meetings. In all studies, EWS interventions provided education to the patient about the nature of bipolar disorder, as well as early warning sign recognition and management, in addition to TAU. The interventions ranged from five sessions (Van Gent 1991) to 221 sessions (Colom 2003c; Colom 2003b). The interventions for managing EWS, once recognised by the patient, ranged from complex individual approaches such as cognitive therapy (e.g. Lam 2003, Scott 2006) to simple individual approaches that involved seeking an urgent appointment with health professionals (Perry 1999), and also group and family focused psychoeducation (e.g. Colom 2003c; Colom 2003c; Miklowitz 2000). There were no studies utilising EWS interventions with intermittent medication.

3.4 Outcomes

3.4.1 Time to any relapse

Six trials reported time to any relapse (Colom 2003c; Colom 2003b; Lam 2003; Miklowitz 2000; Perry 1999; Scott 2006) .

3.4.2 Time to manic/hypomanic or depressive episode

Time to manic/hypomanic or depressive episode were reported by four trials (Colom 2003c; Lam 2005; Perry 1999; Scott 2006) . Another four trials reported time to depressive episode (Colom 2003c; Lam 2003; Perry 1999; Scott 2006) . One trial reported mixed recurrence (Colom 2003c). Some trials (Simon 2004; Lam 2000; Van Gent 1991; Scott 2001) reported outcomes that could not be used due to incomplete information.

3.4.2 Percentage of people hospitalised

These were reported in four of the trials (Colom 2003c; Colom 2003b; Perry 1999; Simon 2004). Lam 2000 reported that mean number of hospitalisations was not significant when adjusted, but did not provide the number of people admitted. Two trials reported on hospitalisation, but did not specify the number of people in control and intervention groups who were hospitalised (Miklowitz 2003; Scott 2001), and hence the data could not be analysed. Number of days spent in hospital was recorded by two trials (Perry 1999; Meyer 2003).

3.4.3 Depressive symptoms

Lam 2000 and Lam 2003 reported on depressive symptoms measured by the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS). Authors of Perry 1999 and Scott 2006 supplied us with HDRS scores and Scott 2006 supplied BDI scores. Data on BDI and HDRS could not be extracted from Lam 2003, because they were incomplete.

3.4.4 Manic symptoms

Authors of Perry 1999 and Scott 2006 provided Bech Rafaelsen Mania Scale (BRMS) scores.

3.4.5 Measure of functioning

Two trials reported on social functioning measured by MRC social performance scale (Lam 2000; Perry 1999). Scott 2001reported functioning by Global Assessment of Function (GAF) and Work and Social Adjustment Scale (WASA) scores, but these could not be translated into scores on the MRC social performance scale.

Secondary outcomes of satisfaction with the intervention, quality of life and perceived control over illness, that were outlined in the protocol, could not be analysed due to the absence of complete information in the original reports.

Risk of bias in included studies

For further information please refer to additional Table 1 'Methodological quality of included studies'.

All trials included were randomised controlled trials. Three trials did not report the method of randomisation (Lam 2000; Meyer 2003; Van Gent 1991). Blinding was not easy due to the nature of interventions, and most of the trials had independent outcome assessors, with the exception of three trials (Van Gent 1991; Scott 2001; Meyer 2003). None of the trials reported prospective rating of blinding, except one trial (Miklowitz 2003) in which it was reported that it proved difficult to keep assessors unaware of the patients' psychosocial group assignments. It was stated in nine trials that an intention to treat analysis (ITT) was undertaken. Two trials did not state whether an ITT analysis had been performed (Scott 2001;Van Gent 1991).

Six studies were scored as category A (Adequate) for concealment of allocation, four of the studies (Miklowitz 2003; Scott 2001; Van Gent 1991; Lam 2000) were scored as category B (Unclear), and an ongoing study (Meyer 2003) was also scored as B. Please refer to additional Table 1 for details on individual trials.

Effects of interventions

1. The search

Out of the 11 included studies, only six studies reported the primary outcomes outlined in the protocol for this review (Colom 2003c; Colom 2003b; Lam 2005; Miklowitz 2003; Perry 1999; Scott 2006). One trial reported only secondary outcomes outlined in the protocol (Simon 2004). Three of the studies did not report any outcomes that could be used (Scott 2001;Van Gent 1991; Meyer 2003).

2. Primary outcomes (Table 2)

2.1 Time to first recurrence of any type

Data were available from six trials. The pooled estimate was significant favouring the EWS intervention group (random effects, hazards ratio 0.57, 95% CI 0.39 to 0.82), but the results showed heterogeneity (chi^2 =16.23, df =5, p=0.006, I-squared = 69.2%).

2.2 Time to manic/hypomanic episode

Data were available from four trials. The pooled estimate was almost significant favouring the EWS intervention group (random effects, hazards ratio 0.66, 95% CI 0.40 to 1.06), but the results showed heterogeneity (chi^2=9.29, df =3, p=0.03, I-squared = 67.7%).

2.3 Time to depressive episode

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Data were available from four trials. The pooled estimate was significant favouring the EWS intervention group (random effects, hazards ratio 0.57, 95% CI 0.33 to 0.99), but the results showed heterogeneity (chi^2 =11.97, df =3, p=0.007, I-squared =74.9%).

3. Secondary outcomes (Table 2)

3.1 Percentage of people hospitalised

Four trials reported this outcome (Perry 1999; Colom 2003c; Colom 2003b; Simon 2004). The pooled estimate was significant favouring the EWS intervention group (fixed effect, RR 0.67, 95% CI 0.47 to 0.95), and the results showed little heterogeneity (chi ^{2}=3.03, df =3, p =0.39, I-squared=1.0%). We intended to do a best/worse case scenario, but there was only one missing set of data values (one of the participants died), and the best/worse case scenario did not make any significant difference to the conclusions.

3.2 Measure of depressive symptoms

3.2.1 BDI Scale

Post measurement data were obtained from two studies (Lam 2000; Scott 2006). The data showed characteristics of being skewed and were therefore not entered into a meta-analysis. The data (means and standard deviations for each treatment groups) were entered into an additional table (Table 3), and no formal statistical analyses were applied. For the next issue of the review, we intend to contact the authors of the studies to obtain data on change from baseline for each of the groups.

3.2.2 HDRS scale

Post measurement data were obtained from three studies (Lam 2000; Perry 1999;Scott 2006). The data showed characteristics of being skewed, and therefore were not entered into a meta-analysis. The data (means and standard deviations for each treatment groups) were entered into an additional table (Table 4), and no formal statistical analyses were applied. For the next issue of the review, we intend to contact the authors of the studies to obtain data on change from baseline for each of the groups.

3.2.3 BRMS

Post measurement data were obtained from two studies (Perry 1999; Scott 2006). The data showed characteristics of being skewed, and therefore were not entered into a meta-analysis. The data (means and standard deviations for each treatment groups) were entered into an additional table (Table 5), and no formal statistical analyses were applied. For the next issue of the review, we intend to contact the authors of the studies to obtain data on change from baseline for each of the groups.

3.3.1 MRC Social Performance

This was reported by two studies (Lam 2000; Perry 1999). Post measurement data were obtained from one study (Lam 2000). The data showed characteristics of being skewed and therefore were not entered into a meta-analysis. The data (means and standard deviations for each treatment groups) were entered into an additional table (Table 6), and no formal statistical analyses were applied. For the next issue of the review we intend to contact the authors of the study to obtain data on change from baseline for each of the groups. Change from baseline data was reported by one study (Perry 1999) at three time points (6 months, 12 months and 18 months). There was no statistical difference in scores between the two treatment groups at 6 and 12 months, but a statistical difference was reported between the two groups at 18 months.

4. Heterogeneity

We examined heterogeneity at various levels in those studies that contributed primary outcome data on time to first bipolar episode.

4.1 Comparison of studies that included psychological component without EWS in TAU and those that had only TAU in control groups

Four of the trials included TAU alone for the control group (Lam 2005; Perry 1999; Scott 2006; Miklowitz 2003). Two studies included psychological intervention that did not include EWS component along with TAU (Colom 2003c; Colom 2003b) to control for the non-specific effects of psychological treatment, including time spent with therapists.

The sub-group analysis for time to any recurrence can be seen in Figure 02 02, and the results are presented in Table 7. The meta-regression analysis showed no significant difference for this factor (Table 8).

Time to manic/hypomanic episode (Table 9) was reported by three of the above non-psychological TAU trials (Perry 1999; Lam 2003; Scott 2006) and one of the non-EWS psychological group TAU trials (Colom 2003c). The sub-group analysis can be seen in Figure 02 02. A meta-regression was not carried out for this factor, due to the lack of information in a number of studies.

Time to depressive episode (Table 10) was reported by three non-psychological TAU studies (Perry 1999; Scott 2006; Lam 2003) and one of the psychological TAU studies (Colom 2003c). The sub-group analysis can be seen in Figure 02 03. A meta-regression was not carried out for this factor, due to the lack of information in a number of studies.

4.2 Time to first recurrence of any type for TAU vs enhanced TAU in control group

In Graph 02 01, we compared time to first recurrence of any type for psychological +TAU Vs non psychological +TAU (section 4.1). Three of the non-psychological TAU trials (Perry 1999; Lam 2003; Scott 2006) used only TAU ,but one of the trials (Miklowitz 2003) used enhanced TAU with two additional sessions to provide education about bipolar disorder in the community, as well as the non-psychological TAU delivered to patients with bipolar disorder as part of routine care . The sub-group analysis can be seen in Figure 02 04. A meta-regression was not carried out for this factor due to the lack of information in a number of studies.

4.3 Time to first recurrence of any type for Intervention delivered in groups vs individually (Table 11)

Three trials delivered the intervention in groups (Colom 2003c;

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Colom 2003b; Miklowitz 2003) and other three delivered it individually (Perry 1999; Lam 2003; Scott 2006). The results from the sub-group analysis can be seen in Figure 02 05. The meta-regression analysis showed no significant difference for this factor (Table 8).There were insufficient data to compare time to manic/hypomanic and depressive episodes.

4.4 Time to any recurrence for patients stabilised for at least one month after last acute bipolar episode vs patients recruited during or immediately after (< one month) acute bipolar episode (Table 12)

One of the studies (Scott 2006) recruited patients in an acute bipolar episode and another (Miklowitz 2003) included patients immediately after an acute bipolar episode. The sub-group analysis can be seen in Figure 02 06. The meta-regression analysis showed no significant difference for this factor (Table 8). Heterogeneity was abolished, and EWS interventions were effective in reducing time to the next bipolar episode in trials confined to patients recruited at least one month after remission from an acute bipolar episode. There were insufficient data to explore the effects on manic/hypomanic episode or depressive episodes.

4.5 Simple vs complex interventions for EWS

One study examined only the recognition of EWS and seeking help early from health professionals (Perry 1999). The other five studies (Colom 2003c; Colom 2003b; Lam 2003; Scott 2006; Miklowitz 2000) provided the patient and/or family with more complex plans of management for EWS once they were recognised, plus additional help for managing bipolar disorder. The results for time to first recurrence of any type are shown in Table 13 and the sub-group analysis can be seen in Figure 02 07.

There was an insufficient number of studies in one of the sub-groups to perform a meta-regression.

Time to manic/hypomanic episode results are reported in Table 14 and time to depressive episode are shown in Table 15. The sub-group analyses can be seen in Figures 02 08 and 02 09 respectively. There was an insufficient number of studies in one of the sub-groups to perform a meta-regression.

4.6 EWS interventions where the primary focus is EWS versus interventions where EWS is not the primary focus of the intervention

Five studies were judged to have a primary focus on EWS interventions on the basis of the time devoted to the EWS interventions, the teaching of the EWS intervention early in the treatment and/or the emphasis given to the intervention in the authors' description of the intervention (Colom 2003c; Colom 2003b; Lam 2003; Miklowitz 2000; Perry 1999). Only one study was judged to include EWS, but not as the primary focus of the intervention (Scott 2006).

The results for the time to first recurrence of any type can be seen in Table 16 and in Figure 02 10. There was an insufficient number of studies in one of the sub-groups to perform a meta-regression.

The results for time to manic/hypomanic episode and time to depressive episode can be seen in Table 17 and Table 18, and the sub-group analyses can be in Figures 02 11 and 02 12. For both analyses there was an insufficient number of studies in one of the sub-groups to perform a meta-regression.

DISCUSSION

There were clinically important findings from the meta-analysis, namely that time to first relapse of any type, time to manic/hypomanic episode and time to depressive episode favoured the EWS intervention group. Two other clinically relevant findings were the percentage of people hospitalised and measure of functioning, which also favoured the EWS intervention group. However the data on functioning were sparse, based on one relatively small RCT, and only favoured the EWS intervention group at 18 months. In the protocol we had aimed to look at the effectiveness of intermittent medication used on recognition of EWS but there were no studies which satisfied our inclusion criteria. Measures of depressive and hypomanic symptoms did not show any effects of EWS interventions, suggesting that the effects on function may not be related to reducing symptoms that remain between acute bipolar episodes. Treatment that has an impact on depressive and manic type symptoms between acute bipolar episodes are highly desirable, given that people with bipolar disorder have these symptoms between 30-50 per cent of the time (Judd 2002). Most of the participants in this analysis had a diagnosis of Bipolar I, and there were very few with Bipolar II diagnosis. The results of this analysis may not apply to Bipolar II patients.

Some of the pooled estimates showed substantial heterogeneity . However, the forest plots show that they are quantitative rather than qualitative, with the direction of effect favouring the EWS intervention group. A consistency in the results favouring EWS interventions, despite variation in trial characteristics, may be used to support the view that the results are generalisable to a variety of clinical settings. Factors that may have influenced the heterogeneity were considered and examined (see under Table 1 , Table 19 , Table 20 , Table 21 and forest plots under heterogeneity). The most important factor in terms of investigating heterogeneity was the recruitment in some studies of patients in acute bipolar episode or shortly after the onset of the episode (Scott 2006; Miklowitz 2000). These studies differed from the others, both in patient characteristics and the delivery of the EWS intervention. Scott 2006 employed an intervention where the EWS intervention was not the primary focus of the intervention, while Miklowitz 2000 delivered the intervention through family psychoeducation rather than through targeting the individual. Scott 2006 provided evidence that the number of previous episodes had a bearing on the effectiveness of the psychological intervention involving EWS, with a large number of previous bipolar episodes being associated

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with increased bipolar recurrence and a smaller number of previous bipolar episodes being associated with decreased bipolar recurrence with the psychological intervention. A reanalysis of data from Colom 2003c, reported in Scott 2006a, also confirms that psychoeducation was not effective in patients with more than 12 previous bipolar episodes. However, the patients in Scott 2006 also included those in acute bipolar episode or on immediate remission from an acute bipolar disorder, while a large proportion had other features generally regarded as having an adverse effect on outcome such as convictions or cautions for violence.

A meta-regression for all potential effect modifiers could not be performed due to small number of included studies. Meta-regression for two of the potential effect modifiers was performed. These were (1) the nature of the control group (non-psychological treatment as usual) versus psychological intervention control group and (2) recruited one month or more after episode versus recruited during and soon after episode. The nature of the control group did not explain the heterogeneity, but recruitment of patients during an acute bipolar episode did seem to explain the high degree of heterogeneity in the results. However, there were only a small number of studies included in the analysis. A funnel plot was done to look at publication bias. No conclusions could be made from the funnel plot, due to the small number of studies.

A thorough search strategy was used in this review, which included hand searching of relevant journals. There may still be gaps in the search strategy such as unpublished data (grey literature), which are difficult to get hold of. We included studies where we were confident that an EWS intervention had been attempted. Some trials did not give precise descriptions of the nature of the psychological intervention tested and we did not get a response when we wrote to some authors for clarification. All trials were randomised controlled trials (RCTs), and concealment of allocation was rated as A or B (Table 1) . Three studies (Meyer 2003; Scott 2001; Van Gent 1991) did not report intention to treat analysis. Two studies reported using intention to treat principles (Lam 2000; Lam 2003), but there were missing data that were not accounted for in the final reported outcomes. In all included RCTs, outcomes were not blinded, but were independently and systematically obtained with less than 20 per cent missing data . The follow up period in most trials varied from 12 to 24 months, except one trial (Van Gent 1991) in which participants were followed up for six months. All trials included personality disorder, with the exception of one trial (Lam 2003), and it was not clear in one other trial (Miklowitz 2000). Axis 1 co-morbidity was included in two of the trials (Perry 1999; Scott 2006). Outcome assessments were reported as independent but not blind in all trials except Van Gent 1991. Allocation concealment was adequate for all except two trials (Lam 2000; Miklowitz 2000) providing data for analysis. Some of the studies reported the percentage of people with personality disorders (Colom 2003c; Colom 2003c (a); Perry 1999; Scott 2006), substance abuse or dependence (Perry 1999; Scott 2006), but no conclusions could be drawn concerning the effectiveness of EWS interventions in personality disorder and substance use disorders, because few trials reported outcomes in these patient groups, and individual patient data were not available.

A matter of concern in relation to the robustness of our findings is that five out of 11 RCTs provided no primary outcome data, possibly because they did not find a positive outcome, and introducing bias due to selective reporting of outcome measures (Williamson 2005 a; Hutton 2000). We were unsuccessful in extracting further information on time to relapse on contacting the authors of the other RCTs. These five studies account for 43% (534/1230) of the total number of people randomised, and one trial included 441 participants (Simon 2004). If the data on the primary outcome were available from these studies (two of these studies were pilot studies for larger RCTs that contained data on the primary outcome (Lam 2000;Scott 2001), then it may be possible that the overall conclusion would be closer to showing no difference between the two interventions. Therefore, the results of the analyses need to be interpreted with caution.

The meta-analysis included a substantial number of patients. Time to first recurrence of any type included data from six studies and 690 participants. Time to manic/hypomanic episode included data from four studies and 533 participants. Time to depressive episode had data from four studies and 533 participants. Meta-analysis of percentage of people hospitalised included data from four studies and 679 participants. Less confidence should be placed in the results of EWS interventions on function. The measure of function had data from two studies and 92 participants. The data on hospitalisation comes from four studies involving 679 patients. However, a study with negative clinical outcomes did not provide data on hospitalisation, so again, caution should be applied to this result. The pooled analysis shows clearly for the first time that EWS interventions may reduce the percentage of patients who become hospitalised with an acute bipolar episode. This result may be important because hospitalisation is unpopular with most patients, in short supply and expensive. The savings made from hospitalisation might be used to fund the provision of EWS interventions that are popular with patients, provided they are targeted at patients with bipolar disorder who have a history of hospitalisation.

Unfortunately few trials reported on the secondary outcomes that we planned to look at, and as with the primary outcome, the results of these analyses should be interpreted with caution, due to the possibility of outcome reporting bias. For measures of function, only one trial presented results that could be used in a meta-analysis. Multiple scales were used for the same outcome, and there is no agreement currently on how comparisons can be made between these scales for people suffering from bipolar disorder. Although we aimed to look at outcomes such as measures of satisfaction with the intervention, patient empowerment and quality of life, none of the trials reported on these outcomes. There was inconsistency on how medication use were reported, and hence a meta-analysis

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was not attempted.

In the RCTs reporting the primary outcome, the EWS intervention was delivered to participants only, except in Miklowitz 2003 where the carer was also included. The EWS intervention was delivered in groups (Colom 2003c; Colom 2003b; Miklowitz 2003) and individually (Lam 2005; Perry 1999; Scott 2006) over 12 sessions or more, except for one trial (Van Gent 1991). Perry 1999 was the only trial that used therapists with little previous experience to deliver the intervention. Therefore, successful EWS interventions seem to require around 12 sessions of therapist time and involve therapists of high competency. On this basis, EWS interventions for bipolar disorder may be expensive, although there appears to be a cost offset from reduced hospitalisation and improvements in social function, including patients returning to work. The one EWS intervention that used a less experienced and, therefore, less expensive therapist only showed a benefit against manic type recurrences and function, without any effect against depressive type recurrence. The relative cost-effectiveness of interventions involving more experienced versus less experienced therapists is a topic for further research.

AUTHORS' CONCLUSIONS

Implications for practice

Though data were obtained from a limited number of relevant trials, the results suggests psychological interventions incorporating EWS may be clinically effective in reducing relapse and hospitalisation, and possibly on function. EWS interventions had no impact on depressive and manic symptoms. The meta-analysis revealed an effect of EWS interventions on hospitalisation that was not previously well established. However, nearly half the identified RCTs did not report the primary outcome measure, so there may be a problem with selective reporting against negative outcomes. In general these trials had interventions delivered by therapists with some experience of both psychological intervention and bipolar disorder. An average of about twelve sessions of an hour long duration was used. The only exception to this was Perry 1999, which used a therapist with little previous experience.

Most health services in most countries could not accommodate EWS interventions within their usual treatment plans because of the way services are constructed currently and/or a shortage of staff trained to deliver EWS interventions. However, when psychological interventions for bipolar disorder can be purchased, the evidence in the meta-analysis favours interventions that incorporate the assessment and management of EWS. The cost offset of the EWS interventions through their effectiveness on both hospitalisation and social function including work could mean that EWS interventions for bipolar disorder may be cost effective and worth purchasing. The means by which EWS interventions could be efficiently delivered within existing health service systems is not clearly established.

Implications for research

Research into psychological interventions targeted at preventing recurrence should measure and report time to all bipolar recurrence, time to manic and depressive type recurrences, because these are the target of the intervention, and therefore should be reported as the primary outcome variables. The optimal service delivery of EWS interventions for bipolar disorder in terms of clinical and cost effectiveness and acceptability to service users requires exploration in research. At present, people with bipolar disorder tend to access many different types of service rather than services dedicated to bipolar disorder. EWS interventions may be effective for other patient groups as well; if so, then service delivery of EWS interventions might be efficiently targeted at a wide group of patients, and are more likely to become part of routine care. Another area that needs attention in future research is whether EWS interventions can be usefully applied to patients with bipolar disorder who have had many previous bipolar episodes or those who have just recently remitted from an acute bipolar episode.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Colom 2003b

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : 20 weeks treatment phase, 24 months follow up
Participants	Diagnosis : Bipolar 1 (DSM1V) based on opinion of senior psychiatrist Age - 18 to 65, mean(sd) 34.5(7.8) in treatment and 35.4(10.9) in control Sex 64% females in control , 60% females in treatment group History : Excludes axis 1 comorbidity. Number of previous episodes (7-11) Setting : Secondary care
Interventions	TAU N = 25. seen by their psychiatrist every four weeks. The group met every week in group of eight to twelve patients without any special instruction from same therapists TAU + Psychoeducation (reports as 20 sessions of 90 minutes each. programme delivered by two experienced psychologists) N = 25
Outcomes	Time to any reccurrence,manic reccurence, mixed recurence, depressive recurrence. Percentage of people hospitalised.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Colom 2003c

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : 21 weeks treatment phase, 24 months follow up
Participants	Diagnosis : Bipolar 1 and 11 (DSM1V) based on opinion of senior psychiatrist Age - 18 to 65 Sex - 63% females in control , 63% female in tretment group History : Excludes axis 1 comorbidity. Number of previous episodes (7-11) Setting : Secondary care
Interventions	TAU N = 60. Patients seen by two psychiatrists every four weeks. Control group met every week in groups of eight to twelve without special instructions from the same therapist. TAU + Psychoeducation (21 sessions of 90 minutes . conducted by two experienced psychologist) N =

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Colom 2003c (*Continued*)

	60
Outcomes	Time to any recurrence,manic recurence, mixed recurence, depressive recurrence. Percentage of people hospitalised.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lam 2000

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : Therapy for six months and 12 months follow up
Participants	Diagnosis : Bipolar 1 (DSM1V) , no more details given . Age - 18 to 65, mean(sd) 39.0(10.9)yrs Sex (F :M)12:13 History : Excludes axis 1 comorbidity. Number of previous episodes (7-11) Setting : Secondary care
Interventions	TAU N = 12 delivered by multidisciplinary team . TAU + Psychoeducation (reports as 12 to 20 sessions within six months . Therapists were clinical psychologists with a minimum of six years postqualification experience) N = 13
Outcomes	Mean number of bipolar episodes, depressed episode , hypomanic episode and total bipolar episodes (these couldnt be used)HDRS score at 12 months BDI score at 12 months Measure of functioning
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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Lam 2005

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : 12 to 18 sessions in first six months and two booster sessions in second six months . 24 months follow up
Participants	Diagnosis : Bipolar 1 (DSM1V) based on SCID by research assisstant Age - 18 to 70, mean(sd) 46.4(12.1) in treatment and 41.5(10.8) in control Sex (F :M)28:51 in control , 30:52 in treatment group History : Excludes axis 1 comorbidity. Number of previous episodes (7-11) Setting : Secondary care
Interventions	TAU N = 52 TAU + Psychoeducation (12 to 18 sessions. The therapists were clinical psychologists with a minimum five years post qualification experience.) N = 51
Outcomes	Time to any reccurrence,manic reccurence depressive recurrence. Measure of functioning
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Meyer 2003a

Methods	See table under ongoing studies
Participants	See table under ongoing studies
Interventions	See table under ongoing studies
Outcomes	See table under ongoing studies
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

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Miklowitz 2003

Methods	Allocation : Randomised (2:1) Blinding : None , Outcome assessor blind Duration : nine months treatment , 24 months follow up
Participants	Diagnosis : Bipolar 1 (DSM111-R) using structured psychiatric interview by research assisstant Age - 18 to 60, mean(sd) 35.7(9.2)yrs in treatment group and 35.6(10.6) in control group. Sex (F :M)18:13 in treatment group and 46:24 in control group. History : axis 1 comorbidity - not stated. Number of previous episodes (1-6) Setting : Secondary care
Interventions	TAU N = 70 . This group received two sessions of family education in addition to clinical input / crisis management. TAU + Psychoeducation N = 31 21 sessions of an hour each
Outcomes	Time to any reccurrence. Total number of hospitalization but data couldnt be used as there was no separate data on control and treatment
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Perry 1999

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : 18 months follow up
Participants	Diagnosis : Bipolar 1 and Bipolar 11 (DSM111-R) based on SCID by a trained research asisstant. Age - 18 to 75, mean(sd) 44(13) in treatment and 45(11) in control Sex (F :M)24:11 in control , 23:11 in treatment group History : Includes axis 1 comorbidity. Number of previous episodes (1-6) Setting : Secondary care
Interventions	TAU N = 35 TAU + Psychoeducation (reports as seven to 12 sessions of one hour each by research psychologist with little previous experience) N = 34
Outcomes	Time to any reccurrence,manic reccurence depressive recurrence. HDRS, MRC social functioning scale
Notes	

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Perry 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Scott 2001

Methods	Allocation : Randomised Blinding : None , Outcome assessor blinding unclear Duration : six months treatment . 18 months follow up
Participants	Diagnosis : Bipolar 1 or 11 based on SADS by independent research psychiatrist. Age - > 18 mean(sd) 37.8 (8.7)yrs in treatment group and 40.5 (6.7) in control group. Sex (F :M)14:7 in treatment group and 11:10 in control group. History : includes axis 1 comorbidity. Number of previous episodes (1-6) Setting : Secondary care
Interventions	TAU N = 21 TAU + Psychoeducation (14 sessions of 45 minutes each by two experienced therapists.) N = 21
Outcomes	GAF , ISS , WASA , BDI, Number of patients relapsed. None used.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Scott 2006

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : held weekly for 15 weeks and then with gradually decreasing frequency until 26 weeks. 18 months follow up
Participants	Diagnosis : Bipolar 1 and Bipolar 11 (DSM1V) based on SCID Age - >18 mean(sd) 42.7(11.4) in control and 39.7(10.3) in treatment Sex (F :M)85:40 in treatment , 79:47 in control group History : Includes axis 1 comorbidity. Setting : Secondary care

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Scott 2006 (*Continued*)

Interventions	TAU N = 126 TAU + Psychoeducation (reports as 20 sessions. Delivered by accredited therapists.) N = 127
Outcomes	Time to any reccurence, manic reccurence depressive recurrence. Measure of functioning
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Simon 2004

Methods	Allocation : Randomised Blinding : None , Outcome assessor blind Duration : 12 months follow up
Participants	Diagnosis : Bipolar 1 and 11 (DSM1V) using SCID and record review by senior psychiatrist. Age - > 18 mean(sd) 44.1(13.4)yrs in treatment group and 44.3(12.9) in control group. Sex (F :M)144:212 in treatment group and 157:229 in control group. History : includes axis 1 comorbidity. Number of previous episodes (not stated) Setting : Secondary care
Interventions	TAU N = 229 TAU + Psychoeducation (Five weekly group sessions followed by twice monthly sessions for 12 months) N = 212
Outcomes	Percentage of people hospitalised.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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Van Gent 1991

Methods	Allocation : Randomised Blinding : None Duration : 6 months follow up
Participants	Diagnosis : Bipolar patients (DSM 111 R) based on opinion of two independent psychiatrist. Age - mean(sd) 44(11)yrs in treatment group and 55 (10) in control group. Sex (F :M) - not stated. History : axis 1 comorbidity -not stated. Number of previous episodes - not stated Setting : Secondary care
Interventions	TAU N = 12 TAU + Psychoeducation (reports as five sessions) N = 14
Outcomes	None used
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beardslee 1992	Interventions did not include early signs of recurrence
Beardslee 1993	Duplicate study (same as Beardslee 1992)
Becker 1998	Not RCT
Burns 1994	Population did not include adults with bipolar disorder
Clarkin 1998	Duplicate study (same as Glick 1993)
Cochran 1984	Interventions did not include early signs of recurrence
Draine 1994	Population did not include adults with bipolar disorder
Drake 1996	Intervention did not include early signs of recurrence
Elixhauser 1990	Population did not include adults with bipolar disorder and intervention did not include early signs of recurrence

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(*Continued*)

Frank 2005	Both treatment groups received early warning sign intervention, which is an exclusion criterion in this review
Glick 1993	Intervention did not include early signs of recurrence
Honig 1997	Not RCT
Kochman 2003	Population did not include adults with diagnosis of bipolar disorder
Kornblith 1983	Population did not include adults with diagnosis of bipolar disorder
Lapidus 2001	Interventions did not include early signs of recurrence
Miller 2004	Interventions did not include early signs of recurrence
Monti 1980	Population did not include adults with diagnosis of bipolar disorder and interventions did not include early signs of recurrence
O'Donnell 1999	Interventions did not include early signs of recurrence
Rea 2003	Both control group and treatment group included early signs of recurrence as part of their intervention
Souza 2003	Intervention did not include early signs of recurrence
Tompson 2000	Not an RCT
Tyrer 1992	Population did not include people with early signs of recurrence
Warning 1995	Population did not include adults with diagnosis of bipolar disorder
Weiss 2000	Not RCT
Wolk 1997	Not RCT

Characteristics of ongoing studies *[ordered by study ID]*

Meyer 2003

Trial name or title	Cognitive Behaviour Therapy and Supportive Therapy
Methods	
Participants	Diagnosis : Bipolar 1 or 11 (DSM 1V , SCID) does not say who made the diagnosis. Age : 44.4 (SD==11) in TAU + CBT and 43.5 ((SD=12.7) in TAU. Sex : 47% female in Treatment group and 53% in control Unclear if axis 1 comorbidity was included or excluded. Age :18 - 65 , Mean(sd) 44.4(11) in treatment group and 43.5(12.7) in control group

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Meyer 2003 (*Continued*)

	Sex : 47.4% in treatment group and 52.6% in control group. Setting : Secondary care
Interventions	Interventions : TAU N=38. TAU + Psychoeducation N = 38. Both the groups received psychoeducation plus TAU for 20 sessions of 50 minute each for a period of 9 months. The psychoeducation in control group did not include EWS
Outcomes	Time to any recurrence -not reported. Time to manic episode - not reported Time to depressive episode - not reported HAMD,YMRS, GAS scores at 3 months given . Reported number of days in hospital
Starting date	
Contact information	
Notes	

Poster published in Bipolar Disorders journal and 3 month data was supplied by the Author

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DATA AND ANALYSES

Comparison 1. Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to first recurrence of any type	6	690	Hazards ratio (Random, 95% CI)	0.57 [0.39, 0.82]
2 Time to manic/hypomanic episode	4	533	Hazards ratio (Random, 95% CI)	0.66 [0.40, 1.06]
3 Time to depressive episode	4	533	Hazards ratio (Random, 95% CI)	0.57 [0.33, 0.99]
4 Percentage of people hospitalised	4	679	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.95]
5 Measure of functioning	1	207	Mean Difference (IV, Random, 95% CI)	1.20 [0.30, 2.10]
5.1 MRC social perfomance scale at 6 months	1	69	Mean Difference (IV, Random, 95% CI)	0.43 [-0.76, 1.62]
5.2 MRC social perfomance scale at 12 months	1	69	Mean Difference (IV, Random, 95% CI)	1.24 [-0.07, 2.55]
5.3 MRC social perfomance scale at 18 months	1	69	Mean Difference (IV, Random, 95% CI)	1.97 [0.74, 3.20]

Comparison 2. Heterogeneity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 EWS intervention vs psychological control group for time to first recurrence of any type	6		Hazards ratio (Random, 95% CI)	0.66 [0.48, 0.91]
1.1 EWS intervention	4		Hazards ratio (Random, 95% CI)	0.65 [0.41, 1.03]
1.2 psychological control group	2		Hazards ratio (Random, 95% CI)	0.65 [0.39, 1.09]
2 EWS intervention vs psychological control group for time to manic/hypomanic episode	4		Hazards ratio (Random, 95% CI)	0.65 [0.41, 1.03]
2.1 EWS intervention	3		Hazards ratio (Random, 95% CI)	0.70 [0.39, 1.25]
2.2 Psychological control group	1		Hazards ratio (Random, 95% CI)	0.52 [0.33, 0.82]
3 EWS intervention vs psychological control group for time to depressive episode	4		Hazards ratio (Random, 95% CI)	0.57 [0.33, 0.99]
3.1 EWS intervention	3		Hazards ratio (Random, 95% CI)	0.66 [0.36, 1.22]
3.2 psychological control group	1		Hazards ratio (Random, 95% CI)	0.38 [0.24, 0.62]

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4 Time to first recurrence of any type for TAU Vs enhanced TAU	4	Hazards ratio (Random, 95% CI)	0.65 [0.41, 1.03]
4.1 Studies including only TAU	3	Hazards ratio (Random, 95% CI)	0.76 [0.49, 1.18]
4.2 Studies including enhanced TAU	1	Hazards ratio (Random, 95% CI)	0.38 [0.20, 0.72]
5 Time to first recurrence of any type for Intervention delivered in groups vs individually	6	Hazards ratio (Random, 95% CI)	0.66 [0.48, 0.91]
5.1 intervention delivered individually	3	Hazards ratio (Random, 95% CI)	0.76 [0.49, 1.18]
5.2 intervention delivered in groups	3	Hazards ratio (Random, 95% CI)	0.56 [0.37, 0.87]
6 Inclusion one month after episode vs recruitment during episode	6	Hazards ratio (Random, 95% CI)	0.66 [0.48, 0.91]
6.1 Time to first recurrence of any type for studies recruiting one month after episode	4	Hazards ratio (Random, 95% CI)	0.62 [0.48, 0.80]
6.2 Time to first recurrence of any type for studies recruiting people during episode	2	Hazards ratio (Random, 95% CI)	0.66 [0.24, 1.77]
7 Time to first recurrence of any type for simple VS complex intervention for EWS	6	Hazard ratio (Random, 95% CI)	0.57 [0.39, 0.82]
7.1 Simple intervention for EWS	1	Hazard ratio (Random, 95% CI)	0.74 [0.43, 1.28]
7.2 Complex intervention for EWS	5	Hazard ratio (Random, 95% CI)	0.54 [0.35, 0.83]
8 Time to manic/hypomanic episode for simple Vs complex intervention for EWS	4	Hazards ratio (Random, 95% CI)	0.66 [0.40, 1.06]
8.1 Simple intervention for EWS	1	Hazards ratio (Random, 95% CI)	0.37 [0.18, 0.77]
8.2 Complex intervention for EWS	3	Hazards ratio (Random, 95% CI)	0.76 [0.46, 1.26]
9 Time to depressive episode for simple Vs complex intervention for EWS	4	Hazards ratio (Random, 95% CI)	0.57 [0.33, 0.99]
9.1 Simple intervention for EWS	1	Hazards ratio (Random, 95% CI)	0.63 [0.31, 1.27]
9.2 Complex intervention for EWS	3	Hazards ratio (Random, 95% CI)	0.55 [0.26, 1.13]
10 Time to first recurrence in studies where EWS as primary focus Vs EWS as secondary focus	6	Hazards ratio (Fixed, 95% CI)	0.70 [0.57, 0.85]
10.1 Studies where EWS is the primary focus	5	Hazards ratio (Fixed, 95% CI)	0.58 [0.45, 0.73]

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10.2 Studies where EWS is the secondary focus	1	Hazards ratio (Fixed, 95% CI)	1.05 [0.74, 1.49]
11 Time to manic episode in studies where EWS as primary focus Vs EWS as secondary focus	4	Hazards ratio (Fixed, 95% CI)	0.73 [0.58, 0.93]
11.1 studies where EWS is the primary focus	3	Hazards ratio (Fixed, 95% CI)	0.53 [0.38, 0.74]
11.2 Studies where EWS is the secondary focus	1	Hazards ratio (Fixed, 95% CI)	1.05 [0.74, 1.49]
12 Time to depressive episode in studies where EWS as primary focus Vs EWS as secondary focus	4	Hazards ratio (Fixed, 95% CI)	0.62 [0.48, 0.81]
12.1 Studies where EWS is the primary focus	3	Hazards ratio (Fixed, 95% CI)	0.43 [0.31, 0.61]
12.2 Studies where EWS is the secondary focus	1	Hazards ratio (Fixed, 95% CI)	1.04 [0.69, 1.57]

Analysis 1.1. Comparison 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition, Outcome 1 Time to first recurrence of any type.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

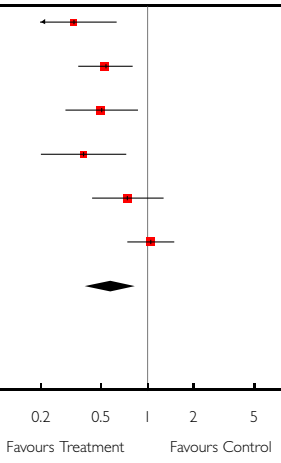
Comparison: 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome: 1 Time to first recurrence of any type

Study or subgroup	TAU N	TAU +Early warning N	log [Hazards ratio] (SE)	Hazards ratio IV,Random,95% CI	Weight	Hazards ratio IV,Random,95% CI
Colom 2003b	25	25	-1.101 (0.324)		14.3 %	0.33 [0.18, 0.63]
Colom 2003c	60	60	-0.6307 (0.209)		19.0 %	0.53 [0.35, 0.80]
Lam 2005	51	47	-0.693 (0.277)		16.1 %	0.50 [0.29, 0.86]
Miklowitz 2003	70	31	-0.968 (0.327)		14.2 %	0.38 [0.20, 0.72]
Perry 1999	35	33	-0.296 (0.277)		16.1 %	0.74 [0.43, 1.28]
Scott 2006	126	127	0.049 (0.178)		20.3 %	1.05 [0.74, 1.49]
Total (95% CI)	**367**	**323**			**100.0 %**	**0.57 [0.39, 0.82]**

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 16.23$, df = 5 (P = 0.01); $I^2 = 69\%$

Test for overall effect: Z = 3.00 (P = 0.0027)



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Analysis 1.2. Comparison 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition, Outcome 2 Time to manic/hypomanic episode.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

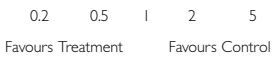
Comparison: 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome: 2 Time to manic/hypomanic episode

Study or subgroup	TAU N	TAU + Early warning N	log [Hazards ratio] (SE)	Hazards ratio IV,Random,95% CI	Weight	Hazards ratio IV,Random,95% CI
Colom 2003c	60	60	-0.653 (0.234)		28.1 %	0.52 [0.33, 0.82]
Lam 2005	46	46	-0.342 (0.319)		23.1 %	0.71 [0.38, 1.33]
Perry 1999	35	33	-0.985 (0.371)		20.4 %	0.37 [0.18, 0.77]
Scott 2006	126	127	0.148 (0.23)		28.4 %	1.16 [0.74, 1.82]
Total (95% CI)	**267**	**266**			**100.0 %**	**0.66 [0.40, 1.06]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 9.29$, df = 3 (P = 0.03); $I^2 = 68\%$

Test for overall effect: Z = 1.71 (P = 0.088)



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Analysis 1.3. Comparison 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition, Outcome 3 Time to depressive episode.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

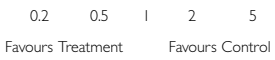
Comparison: 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome: 3 Time to depressive episode

Study or subgroup	TAU N	TAU + Early warning N	log [Hazards ratio] (SE)	Hazards ratio IV,Random,95% CI	Weight	Hazards ratio IV,Random,95% CI
Colom 2003c	60	60	-0.961 (0.244)		27.2 %	0.38 [0.24, 0.62]
Lam 2005	48	44	-0.968 (0.353)		22.2 %	0.38 [0.19, 0.76]
Perry 1999	35	33	-0.461 (0.359)		21.9 %	0.63 [0.31, 1.27]
Scott 2006	126	127	0.039 (0.209)		28.7 %	1.04 [0.69, 1.57]
Total (95% CI)	**269**	**264**			**100.0 %**	**0.57 [0.33, 0.99]**

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 11.97$, df = 3 (P = 0.01); $I^2 = 75\%$

Test for overall effect: Z = 2.01 (P = 0.044)



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Analysis 1.4. Comparison 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition, Outcome 4 Percentage of people hospitalised.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome: 4 Percentage of people hospitalised

Study or subgroup	TAU + Early warning n/N	TAU n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Colom 2003b	2/25	9/25		14.8 %	0.22 [0.05, 0.93]
Colom 2003c	14/60	21/60		34.5 %	0.67 [0.38, 1.18]
Perry 1999	12/33	15/35		23.9 %	0.85 [0.47, 1.53]
Simon 2004	12/212	17/229		26.8 %	0.76 [0.37, 1.56]
Total (95% CI)	**330**	**349**		**100.0 %**	**0.67 [0.47, 0.95]**
Total events: 40 (TAU + Early warning), 62 (TAU)					
Heterogeneity: Chi^2 = 3.03, df = 3 (P = 0.39); I^2 =1%					
Test for overall effect: Z = 2.26 (P = 0.024)					

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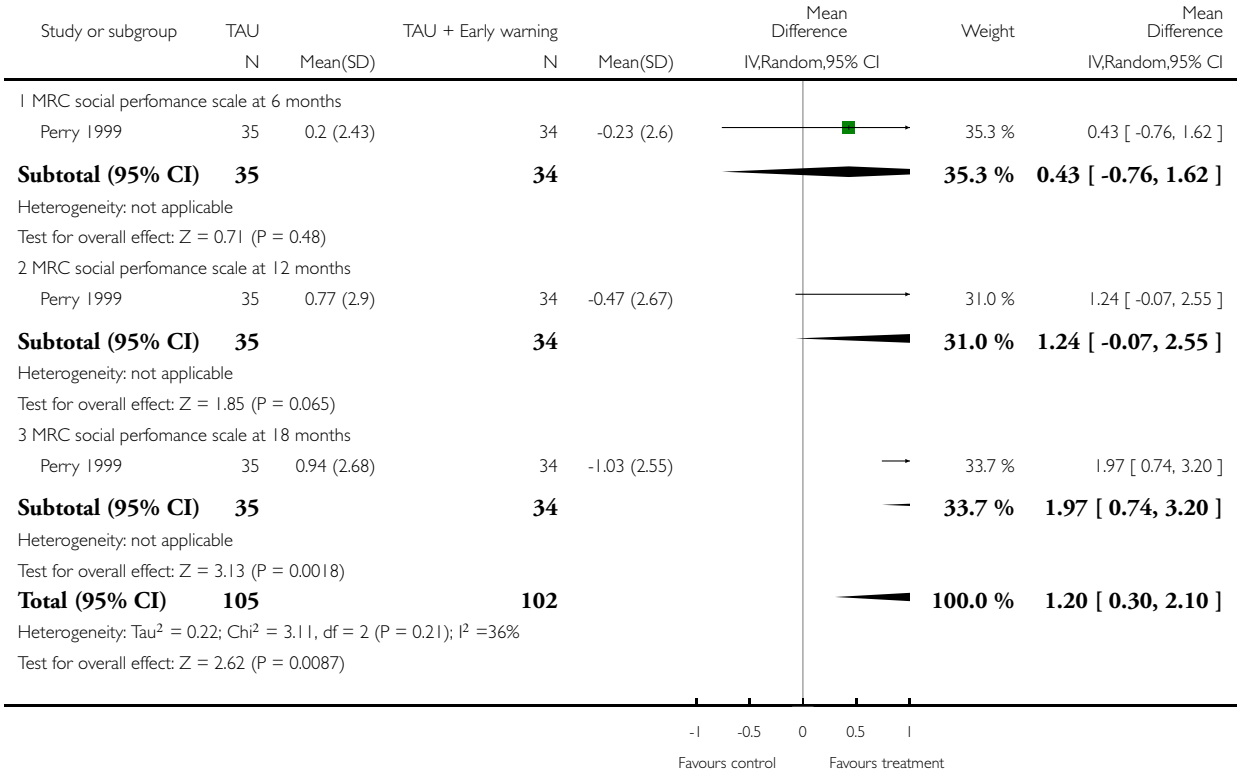
Analysis 1.5. Comparison 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition, Outcome 5 Measure of functioning.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 1 Treatment as usual (TAU) versus TAU and additional early warning sign recognition

Outcome: 5 Measure of functioning



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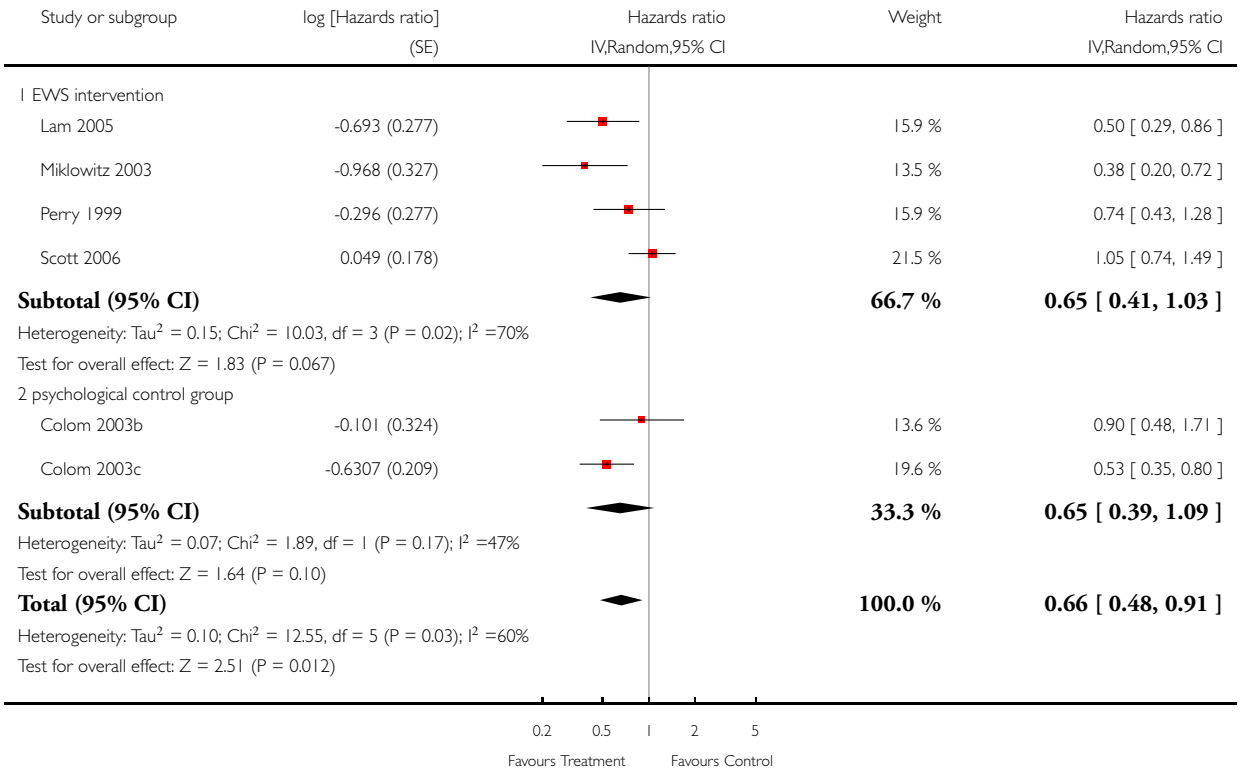
Analysis 2.1. Comparison 2 Heterogeneity, Outcome 1 EWS intervention vs psychological control group for time to first recurrence of any type.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 1 EWS intervention vs psychological control group for time to first recurrence of any type



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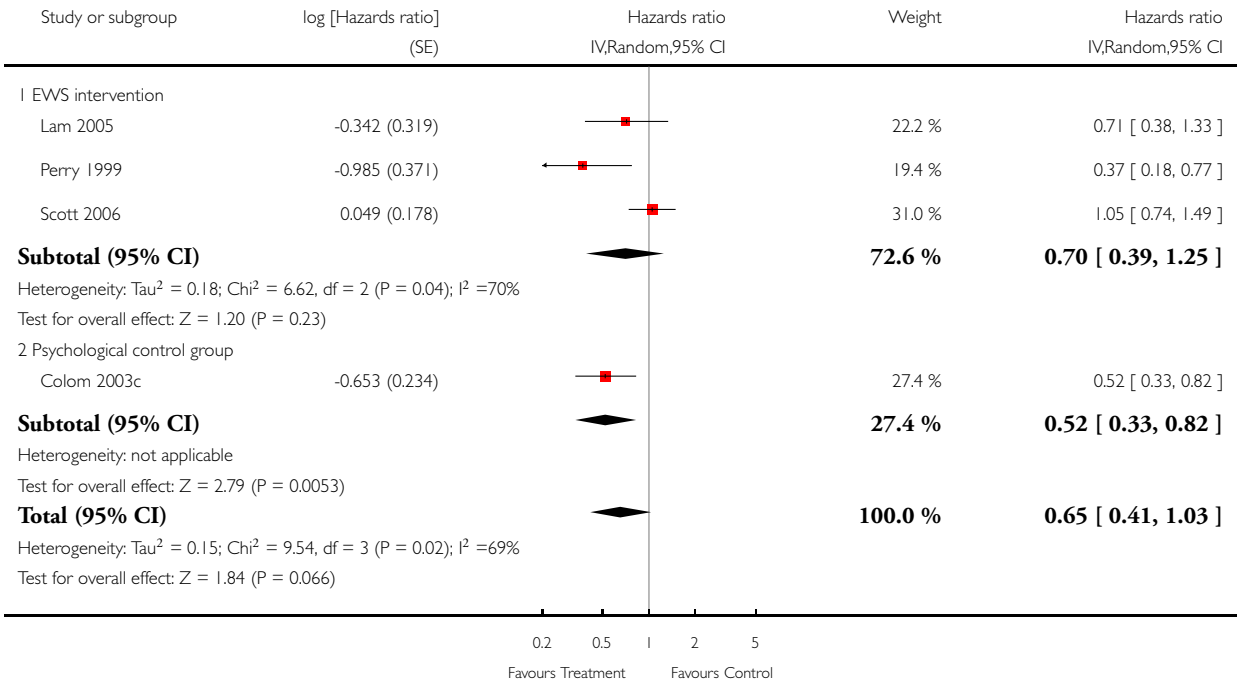
Analysis 2.2. Comparison 2 Heterogeneity, Outcome 2 EWS intervention vs psychological control group for time to manic/hypomanic episode.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 2 EWS intervention vs psychological control group for time to manic/hypomanic episode



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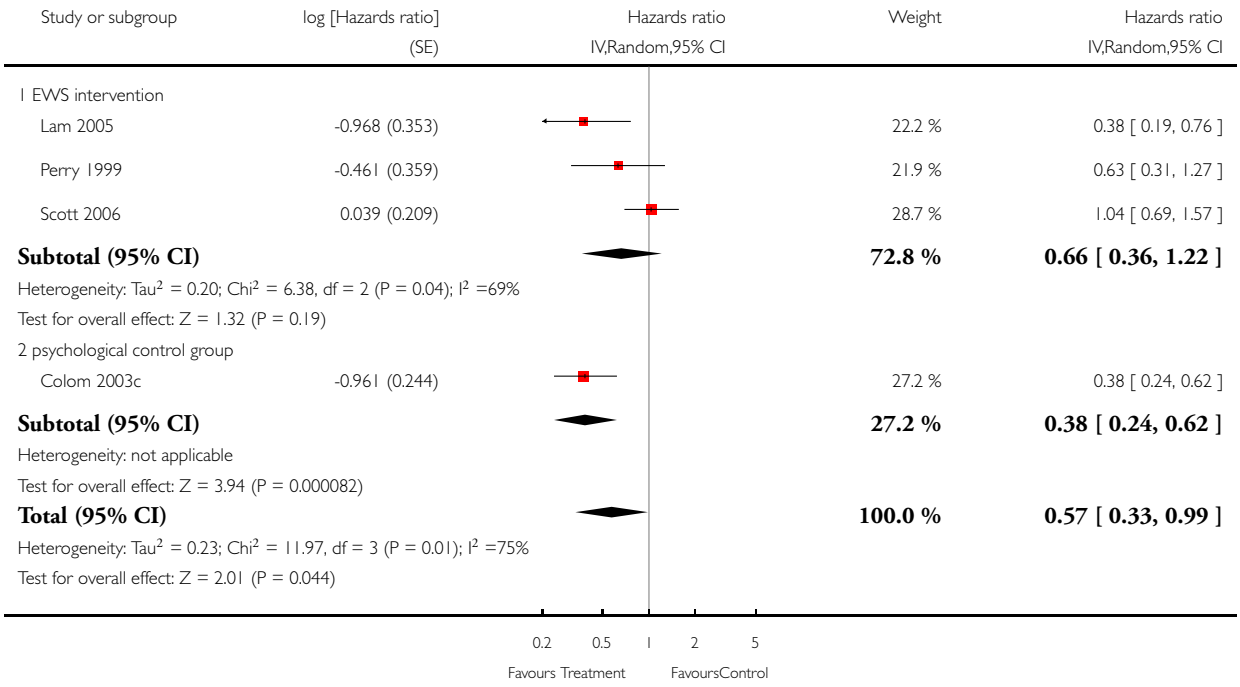
Analysis 2.3. Comparison 2 Heterogeneity, Outcome 3 EWS intervention vs psychological control group for time to depressive episode.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 3 EWS intervention vs psychological control group for time to depressive episode



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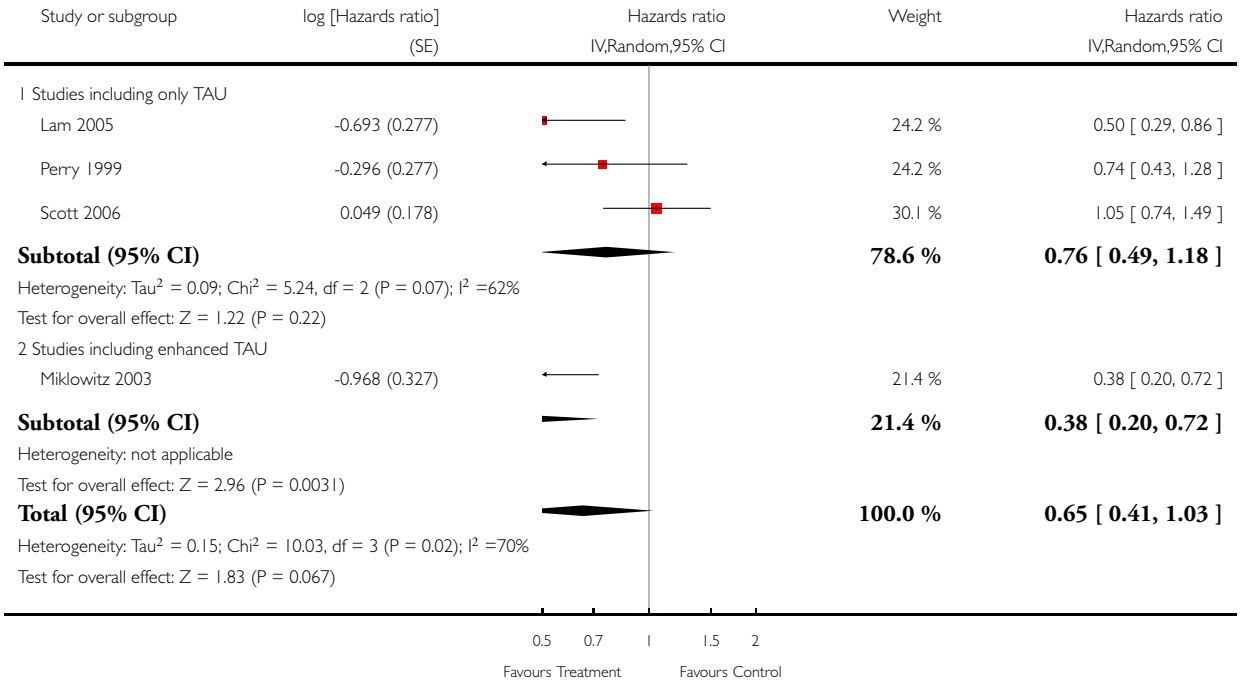
Analysis 2.4. Comparison 2 Heterogeneity, Outcome 4 Time to first recurrence of any type for TAU Vs enhanced TAU.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 4 Time to first recurrence of any type for TAU Vs enhanced TAU



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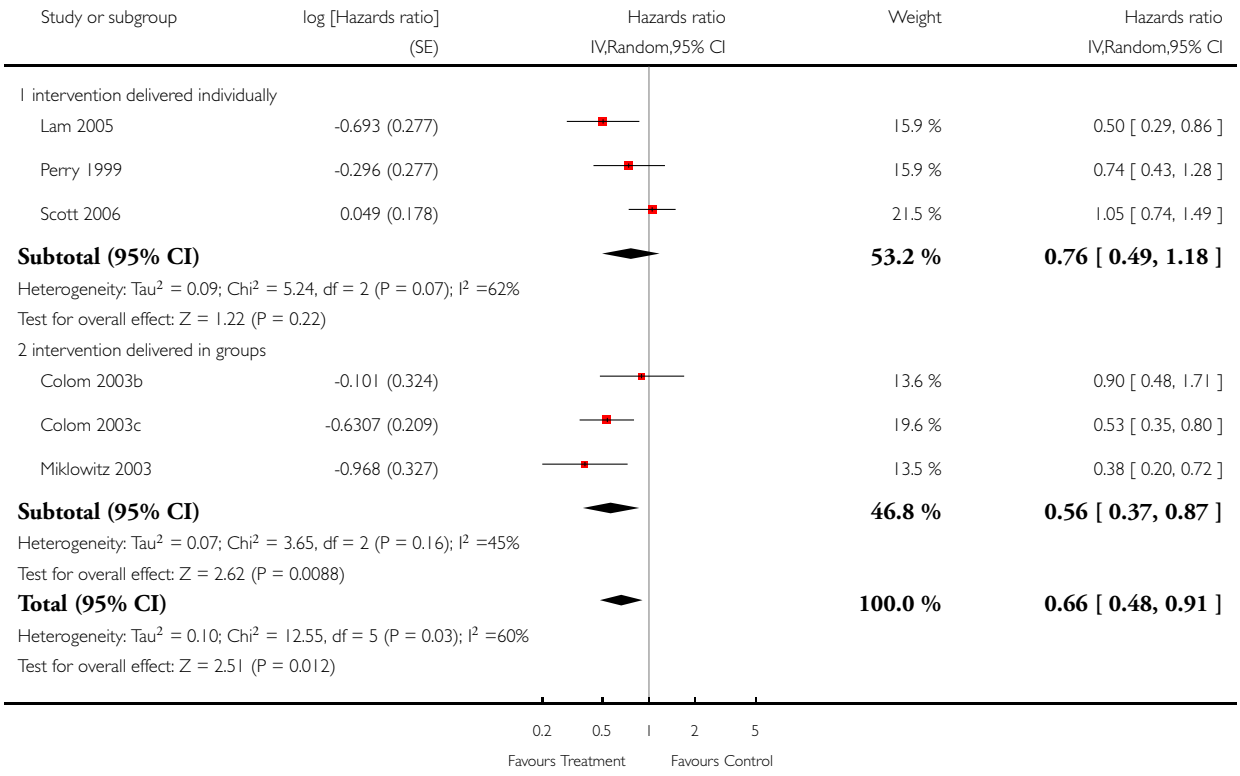
Analysis 2.5. Comparison 2 Heterogeneity, Outcome 5 Time to first recurrence of any type for Intervention delivered in groups vs individually.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 5 Time to first recurrence of any type for Intervention delivered in groups vs individually



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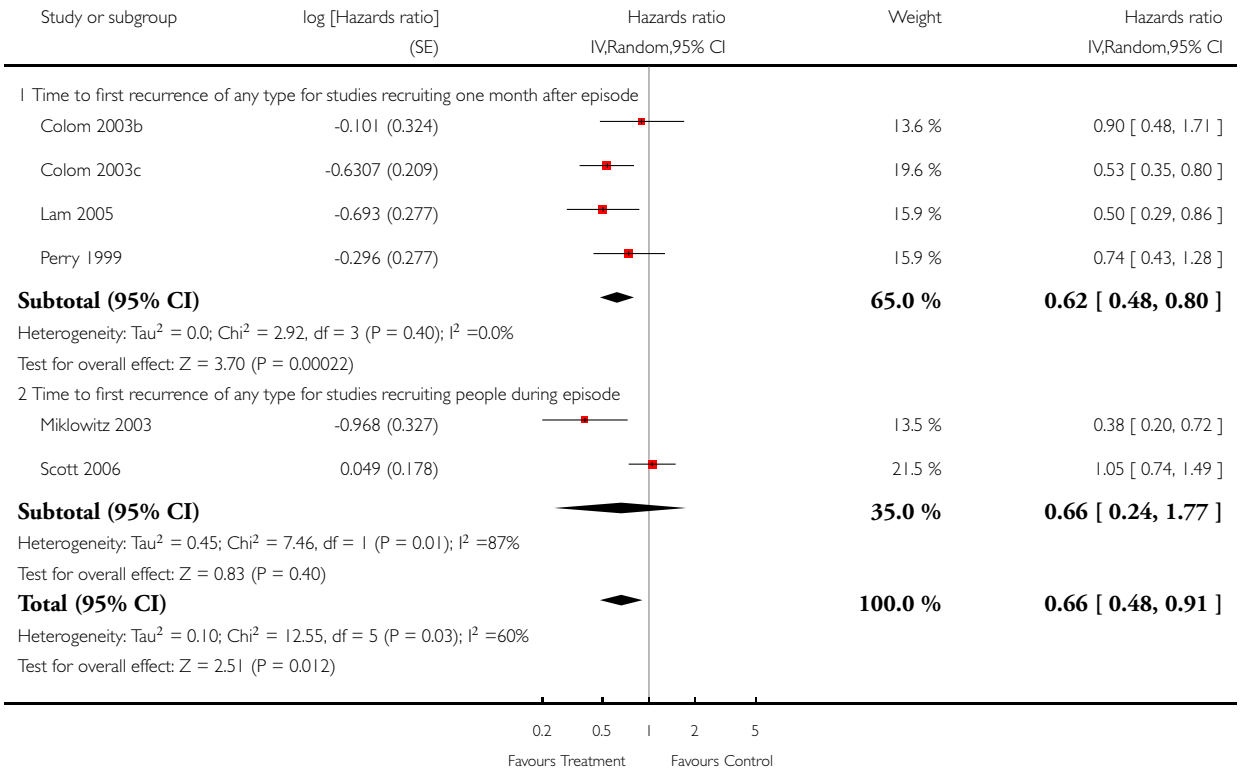
Analysis 2.6. Comparison 2 Heterogeneity, Outcome 6 Inclusion one month after episode vs recruitment during episode.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 6 Inclusion one month after episode vs recruitment during episode



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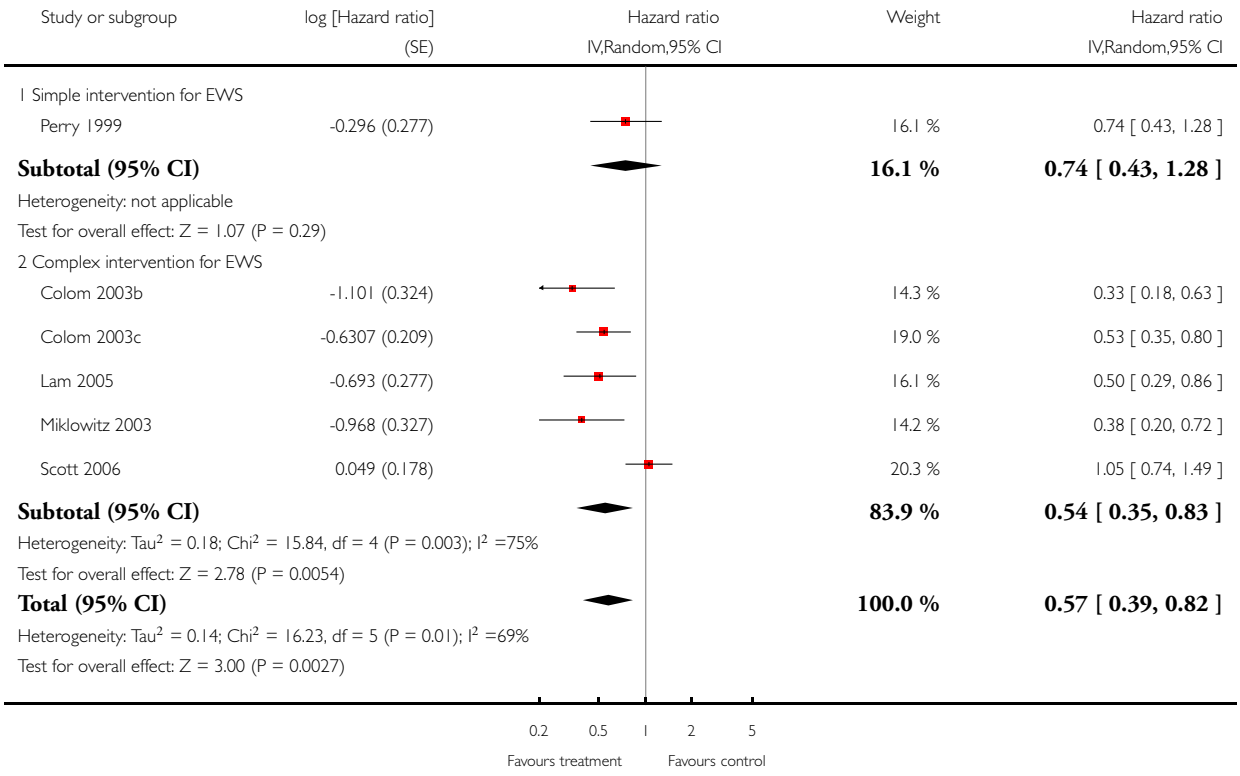
Analysis 2.7. Comparison 2 Heterogeneity, Outcome 7 Time to first recurrence of any type for simple VS complex intervention for EWS.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 7 Time to first recurrence of any type for simple VS complex intervention for EWS



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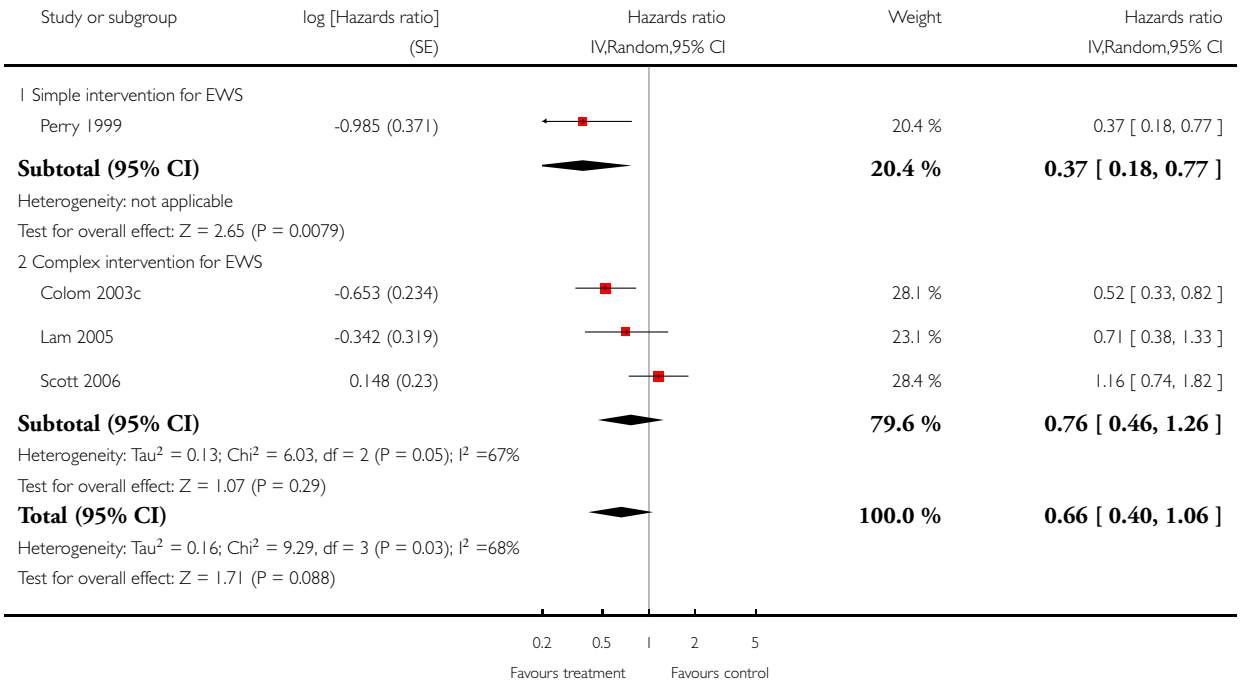
Analysis 2.8. Comparison 2 Heterogeneity, Outcome 8 Time to manic/hypomanic episode for simple Vs complex intervention for EWS.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 8 Time to manic/hypomanic episode for simple Vs complex intervention for EWS



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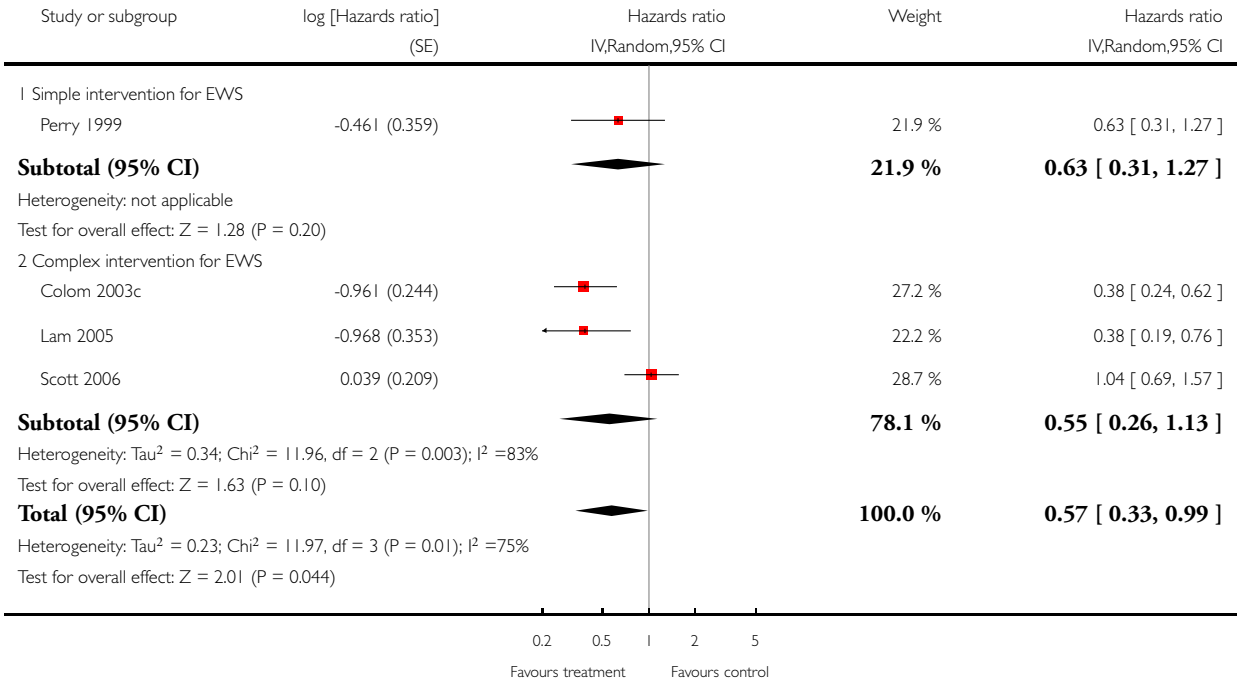
Analysis 2.9. Comparison 2 Heterogeneity, Outcome 9 Time to depressive episode for simple Vs complex intervention for EWS.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 9 Time to depressive episode for simple Vs complex intervention for EWS



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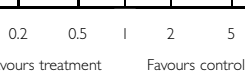
Analysis 2.10. Comparison 2 Heterogeneity, Outcome 10 Time to first recurrence in studies where EWS as primary focus Vs EWS as secondary focus.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 10 Time to first recurrence in studies where EWS as primary focus Vs EWS as secondary focus

Study or subgroup	log [Hazards ratio] (SE)	Hazards ratio IV,Fixed,95% CI	Weight	Hazards ratio IV,Fixed,95% CI
1 Studies where EWS is the primary focus				
Colom 2003b	-0.101 (0.324)		9.6 %	0.90 [0.48, 1.71]
Colom 2003c	-0.6307 (0.209)		23.0 %	0.53 [0.35, 0.80]
Lam 2005	-0.693 (0.277)		13.1 %	0.50 [0.29, 0.86]
Miklowitz 2003	-0.968 (0.327)		9.4 %	0.38 [0.20, 0.72]
Perry 1999	-0.296 (0.277)		13.1 %	0.74 [0.43, 1.28]
Subtotal (95% CI)			**68.2 %**	**0.58 [0.45, 0.73]**
Heterogeneity: Chi^2 = 4.81, df = 4 (P = 0.31); I^2 =17%				
Test for overall effect: Z = 4.53 (P < 0.00001)				
2 Studies where EWS is the secondary focus				
Scott 2006	0.049 (0.178)		31.8 %	1.05 [0.74, 1.49]
Subtotal (95% CI)			**31.8 %**	**1.05 [0.74, 1.49]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.28 (P = 0.78)				
Total (95% CI)			**100.0 %**	**0.70 [0.57, 0.85]**
Heterogeneity: Chi^2 = 12.55, df = 5 (P = 0.03); I^2 =60%				
Test for overall effect: Z = 3.59 (P = 0.00033)				
Test for subgroup differences: Chi^2 = 7.74, df = 1 (P = 0.01), I^2 =87%				



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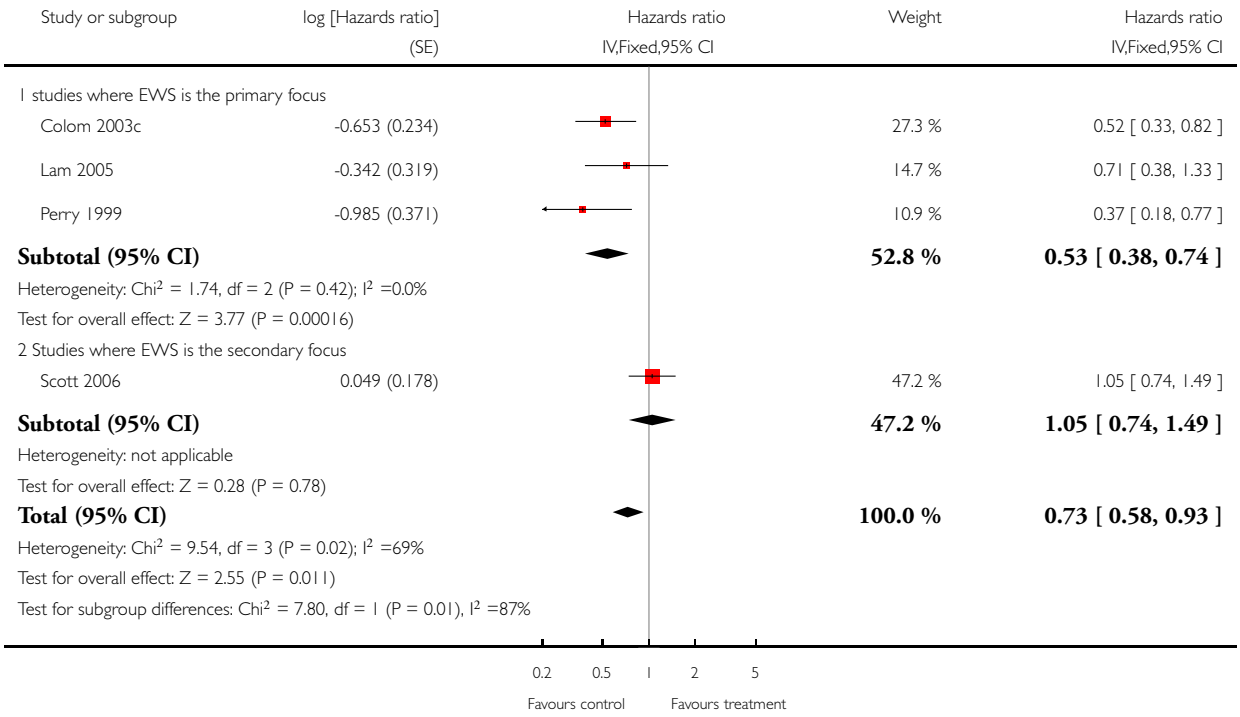
Analysis 2.11. Comparison 2 Heterogeneity, Outcome 11 Time to manic episode in studies where EWS as primary focus Vs EWS as secondary focus.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 11 Time to manic episode in studies where EWS as primary focus Vs EWS as secondary focus



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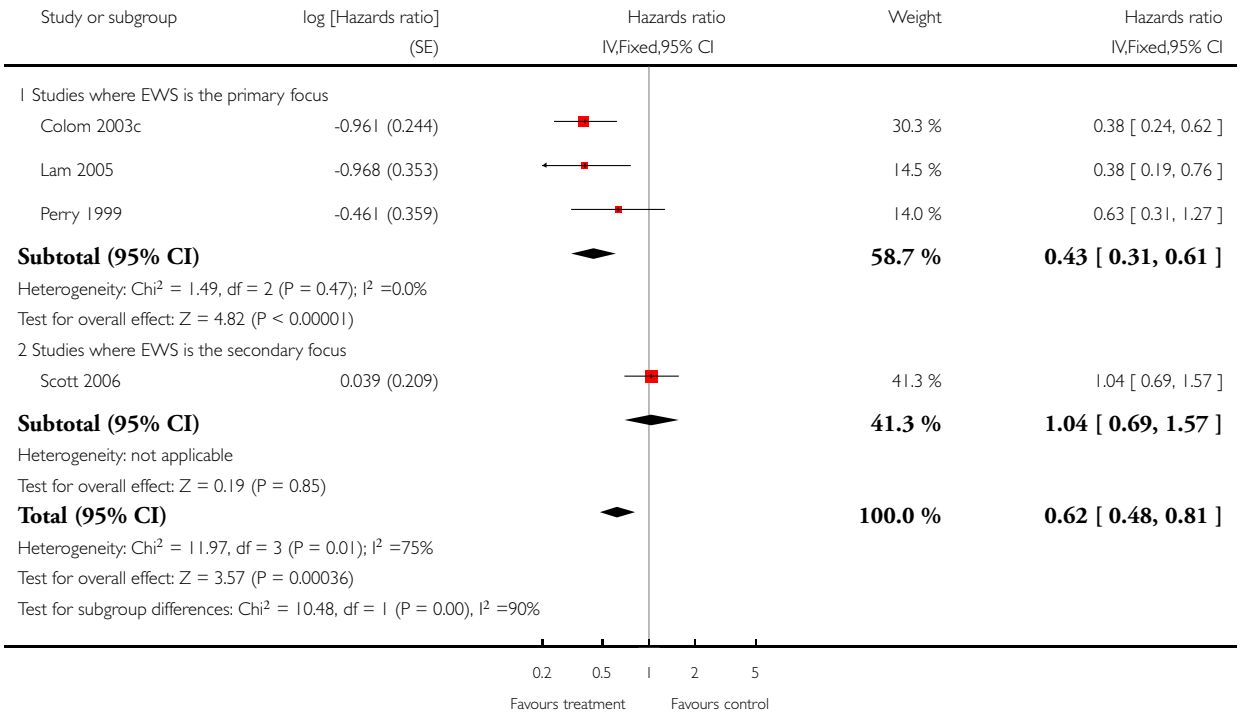
Analysis 2.12. Comparison 2 Heterogeneity, Outcome 12 Time to depressive episode in studies where EWS as primary focus Vs EWS as secondary focus.

Review: Interventions for helping people recognise early signs of recurrence in bipolar disorder

Comparison: 2 Heterogeneity

Outcome: 12 Time to depressive episode in studies where EWS as primary focus Vs EWS as secondary focus



ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study	Allocation	Randomisation	Blinding	ITT
Colom 2003	A	by computerised number generator	Only outcome asessor blinded	ITT principle used
Colom 2003 (a)	A	by computerised number generator	Only outcome asessor blinded	ITT principle used
Lam 2005	A	computer generated allocation sequence	Only outcome asessor blinded	reports ITT principle used, but data missing for primary out-

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Table 1. Methodological quality of included studies (*Continued*)

				come and not reported reasons for it
Lam 2000	B	randomisation procedure not described	Only outcome asessor blinded	Reports ITT principle used. Data on two patients who dropped out not reported
Meyer 2003	B	randomisation not described.	not described	ongoing study
Miklowitz 2003	B	ran- domisation by random number table. 2:1 randomisation used	Only outcome asessor blinded	accounted for all patients but does not state whether ITT principle was used
Perry 1999	A	randomly allocated using principles of minimisation	Only outcome asessor blinded	ITT principle used. Data on one patient missing as patient died due to physical cause
Scott 2005	A	independent trialists and biostatistics office allocated patients to two treatment groups using minimisation algorithm	Only outcome asessor blinded	ITT principle used. Results on four people missing and these were included in final analysis
Simon 2004	A	using a concealed table of computer generated random numberswith no blocking or staratification	Only outcome asessor blinded	ITT principle used. In treatment group 199/212 were included for symptom analysis and all included for utilisation analysis. in control group 215/229 were included in symptom analysis and all were included in utilization analysis
Vangent 1991	B	not described	no blinding , unclear if outcome asessor was blinded	All participants accounted for but does not state whether ITT principle was used

Table 2. Comparison 01: TAU vs TAU+EWS

Outcome Title	No of studies	No of participants	Statistical method	Effect size
Time to any relapse	six	690	Hazards ratio random effect 95% CI	0.57 (0.39 , 0.82)
Time to hypomanic / manic relapse	four	533	Hazards ratio random effect 95% CI	0.66 (0.40 , 1.06)

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Table 2. Comparison 01: TAU vs TAU+EWS (*Continued*)

Time to depressive relapse	four	533	Hazards ratio random effect 95% CI	0.57 (0.33 , 0.99)
Percentage of people hospitalised	four	679	Hazards ratio fixed effect 95% CI	1.49 (1.05 , 2.11)

Table 3. BDI score (Mean, SD)

Study	score at (months)	No in C group	No in T group	Control group score	Treatment group scor	Statistical method	Effect size
Lam 2000	six	11	12	7.60 (8.92)	4.83 (6.10)	WMD 95% CI	2.77 (-3.53 , 9. 07)
Lam 2000	Twelve	11	12	11.56 (13.88)	6.18 (8.44)	WMD 95% CI	5.38 (-4.11 , 14.87)
Scott 2006	Six	85	81	9.30 (10.90)	9.40 (11.00)	WMD 95% CI	-0.10 (-3.43 , 3.23)
Scott 2006	Twelve	85	81	8.30 (10.50)	8.00 (8.10)	WMD 95% CI	0.30 (-2.55 , 3. 15)

Table 4. HDRS Score (Mean, SD)

Study	Score at (months)	No in C group	No in T group	Control group score	Treatment group scor	Satistical method	Effect size
Perry 1999	Six	32	25	3.40 (4.00)	4.00 (3.90)	WMD 95% CI	-0.60 (-2.66 , 1.46)
Perry 1999	Twelve	32	25	4.10 (5.30)	3.30 (3.50)	WMD 95% CI	0.80 (-1.49 , 3. 09)
Perry 1999	Eighteen	32	25	3.90 (4.40)	5.00 (6.00)	WMD 95% CI	-1.10 (-3.90 , 1.70)
Lam 2000	Six	11	12	5.30 (6.96)	4.17 (5.39)	WMD 95% CI	1.13 (-3.99 , 6. 25)
Lam 2000	Twelve	11	12	9.40 (9.47)	4.00 (5.66)	WMD 95% CI	5.40 (-1.05 , 11.85)
Scott 2006	Six	91	90	6.20 (6.20)	5.40 (5.60)	WMD 95% CI	0.80 (-0.92 , 2. 52)

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Table 4. HDRS Score (Mean, SD) (*Continued*)

Scott 2006	Twelve	91	90	6.10 (6.90)	6.30 (5.70)	WMD 95% CI	-0.20 (-2.04 , 1.64)
Scott 2006	Eighteen	91	90	6.00 (6.30)	7.10 (6.70)	WMD 95% CI	-1.10 (-3.00 , 0.80)

Table 5. BRMS Score (Mean, SD)

Study	Score at (months)	No in C group	No in T group	Control group scores	Treatment group scor	Satistical method	Effect size
Perry 1999	Six	25	32	0.30 (0.70)	0.40 (1.10)	WMD 95% CI	-0.10 (-0.57 , 0.37)
Perry 1999	Twelve	25	32	0.04 (0.20)	0.50 (1.30)	WMD 95% CI	-0.46 (-0.92 , 0.00)
Perry 1999	Eighteen	25	32	0.20 (0.70)	0.40 (1.30)	WMD 95% CI	-0.20 (-0.73 , 0.33)
Scott 2006	Six	90	91	5.40 (5.60)	6.20 (6.20)	WMD 95 % CI	-0.15 (-0.60 , 0.30)
Scott 2006	Twelve	90	91	6.30 (5.70)	6.10 (6.90)	WMD 95%CI	0.20 (-1.64 , 2. 04)
Scott 2006	Eighteen	90	91	1.70 (2.60)	2.00 (3.90)	WMD 95%CI	-0.30 (-1.26 , 0.66)

Table 6. MRC perfomance score (Mean, SD)

Study	Score at (months)	No in C group	No in T group	Control group score	Treatment group scor	Statistical method	Effect Size
Lam 2000	Six	11	12	0.31 (0.27)	0.10 (0.11)	WMD 95%CI	0.21 (0.04 , 0. 38)
Lam 2000	Twelve	11	12	0.33 (0.29)	0.09 (0.16)	WMD 95% CI	0.24 (0.05 , 0. 43)

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Table 7. Comparison 02 01

Outcome title	No of studies	No of participants	Statistical method	Effect size
time to recurrence of any type for TAU + EWS intervention in control group	4	520	hazards ratio , random effect , 95% CI	0.65 (0.41 , 1.03)
time to recurrence of any type for TAU + psychological intervention in control group	2	170	hazards ratio , random effect , 95% CI	0.65 (0.39 , 1.09)

Table 8. Meta-regression analyses

Factor	Number of Studies	Slope Estimate	95% CI	p-value
Non-psychological / psychological intervention	6	0.018	(-0.727 to 0.762)	0.963
Inclusion six month after episode / during and immediately after episode	6	0.979	(0.615 to 0.81)	0.788

Table 9. Comparison 02 02

Outcome title	No of studies	No of participants	Statistical method	Effect size
time to manic / hypomanic relapse for TAU + EWS intervention	3	413	hazards ratio , random effect , 95% CI	0.70 (0.39 , 1.25)
time to manic / hypomanic relapse for TAU + psychological intervention	1	120	hazards ratio , random effect , 95% CI	0.52 (0.33 , 0.82)

Table 10. Comparison 02 03

Outcome title	No of studies	No of participants	Statistical method	Effect size
time to depressive episode for TAU + EWS intervention	3	413	hazards ratio , random effect , 95% CI	0.66 (0.36 , 1.22)

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Table 10. Comparison 02 03 (*Continued*)

time to depressive episode for TAU + psychological intervention	1	120	hazards ratio , random effect , 95% CI	0.38 (0.24 , 0.62)

Table 11. Comparison 02 05

Outcome title	No of studies	No of participants	Statistical method	Effect size
Time to first recurrence of any type for intervention delivered individually	3	419	hazards ratio , random effect , 95% CI	0.76 (0.49 , 1.18)
Time to first recurrence of any type for intervention delivered in groups	3	271	hazards ratio , random effect , 95% CI	0.56 (0.37 , 0.87)

Table 12. Comparison 02 06

Outcome title	No of studies	No of participants	Statistical method	Effect size
Time to first recurrence for any type in those studies which recruit patients one month after episode	4	336	hazards ratio , random effect , 95% CI	0.62 (0.48 , 0.80)
Time to first recurrence for any type in those studies which recruit patients during episode	2	354	hazards ratio , random effect , 95% CI	0.66 (0.24 , 1.77)

Table 13. Comparison 02 07

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
Time to first recurrence of any type in those studies with simple intervention for EWS	1	68	Hazards ratio , Random effect 95% CI	0.74 (0.43 , 1.28)
Time to first recurrence of any type in those studies with complex inter-	5	622	Hazards ratio , Random effect 95% CI	0.54 (0.35 , 0.83)

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Table 13. Comparison 02 07 (*Continued*)

vention for EWS				

Table 14. Comparison 02 08

Otcome title	No. of studies	No. of participants	Statistical method	Effect size
Time to manic / hypomanic episode for studies with simple intervention for EWS	1	68	Hazards ratio , random effect 95% CI	0.37 (0.18 - 0.77)
Time to manic / hypomanic episode for studies with complex intervention for EWS	3	465	Hazards ratio , random effect 95% CI	0.76 (0.46 - 1.26)

Table 15. Comparison 02 09

Outcome title	No of studies	No of participants	Statistical method	Effect size
Time to depressive episode in those studies with simple intervention for EWS	1	68	Hazards ratio , random effect 95% CI	0.63 (0.31 - 1.27)
Time to depressive episode in those studies with complex intervention for EWS	3	465	Hazards ratio , random effect 95% CI	0.55 (0.26 - 1.13)

Table 16. Comparison 02 10

Otcome title	No. of studies	No. of participants	Statistical method	Effect size
Time to first recurrence of any type where Ews was the primary focus of intervention	5	437	Hazards ratio , random effect , 95%CI	0.58 (0.45 - 0.73)
Time to first recurrence of any type where EWS was secondary focus of intervention	1	253	Hazards ratio , random effect , 95%CI	1.05 (0.74 - 1.49)

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Table 17. Comparison 02 11

Outcome title	No of studies	No of participants	Statistical method	Effect size
Time to manic / hypomanic episode for studies where EWS was used as primary focus of the intervention	3	280	Hazards ratio , random effect , 95% CI	0.53 (0.38 - 0.74)
Time to manic / hypomanic episode for studies where EWS was used as secondary focus of the intervention	1	253	Hazards ratio , random effect , 95% CI	1.05 (0.74 - 1.49)

Table 18. Comparison 02 12

Outcome title	No of studies	No of participants	Statistical method	Effect size
Time to depressive episode in studies which used EWS as primary focus of intervention	3	280	Hazards ratio , random effect , 95% CI	0.43 (0.31 - 0.61)
Time to depressive episode in studies which used EWS as primary focus of intervention	1	253	Hazards ratio , random effect , 95% CI	1.04 (0.69 - 1.57)

Table 19. Comparison of baseline demographics of studies that reported primary outcomes

Study ID	Colom 2003	Colom 2003 (a)	Lam 2005	Perry 1999	Scott 2005	Miklowitz 2003
AGE	18 -65	18-65 , mean (sd) 34.5 (7.8) in T and 35.4 (10. 9) in C	18-70 , mean (sd) 46.4(12.1) in Treatment and 41.5 (10.8) in Control	18-75 , mean (sd) 44(13) in Treatment and 45 (11) in Control	>18 mean (sd) 42.7(11.4) in C and 39.7 (10.3) in T	18-60,mean (sd) 35.7(9.2) in T and35.6(10.6) in C
GENDER	63.3%females in control, 63.3%females in treatment	F:M (15:10) in control , (16:9) in treatment	F:M (28:51) in control , (30:52) in treatment	F:M (24:35) in control , (23:34) in treatment	F:M(85:127) in T And 79:126 in C	F:M(18:31) in TAnd (46:72) in C
REFERRAL SOURCE	Secondarycare	secondary care	secondary care	secondary care	Secondary care	Secondary care

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Table 19. Comparison of baseline demographics of studies that reported primary outcomes (*Continued*)

MARITALSTATUS	Not stated	Not stated	Not stated	22/34 in treatment and 21/35 in control were married or cohabiting	Cohabiting56/126 in C and46/127 in T	Not clear but requiredContact with carer
IN EPISODEOR NOT	Euthymic only	Euthymic only	currently not fulfilling bipolar disorder criteria	Euthymic	Yes , except mania	Recruited shortly after Onset of acute episode but proportion unclear
HOW LONG FROM PREVIOUS EPISODE	In remission For atleast6 months	At least six months	Not stated	mean (sd) in weeks 25(16) in treatment and 25 (18) in control	Included those inEpisode exceptMania.	Most in episode
NUMBER OF PAST EPISODE	7-11	7-11	7-11	1-6	2-6 episodes (39 in C and 35 in T) 7-11 episodes (29 in C and 25 in T) 12-29 episode (27 in C and 32 in T) 30 + episode (31 in C and 35 in T)	1-6
SUBSTANCE MISUSE	Not stated	Not stated	excluded	included	included	Excluded substanceAbuse and dependenceIn last 6 months
RAPID CYCLING	Included, Unclear what proportion	Not stated	Not stated	Not stated	excluded	not stated
PERSONALITY DISORDER	included	included	excluded	included	included	not clear
PHYSICAL ILLNESS	Not stated	Not stated	Not stated	Not stated	Not stated	excluded neurological problems , others not clear

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Table 19. Comparison of baseline demographics of studies that reported primary outcomes (*Continued*)

PSYCHOTIC SYMPTOMS	Present, 42/60In C and 47/60 In T , P=NS	Present, 19/25 In Control and 23/25 In Treatment , P=NS	Not stated	Not stated	Not stated	not clear
SUICIDE ATTEMPTS	yes	Not stated	Not stated	Not stated	Not stated	not clear
AXIS 1 COMORBIDITY	excluded	excluded	excluded	included	included	not clear

Table 20. Comparison of focus of intervention of studies that reported primary outcome

Study ID	Colom 2003	Colom 2003(a)	Lam 2005	Perry 1999	Scott 2005	Miklowitz 2003
EWS as primary Focus	yes	yes	yes	yes	no	yes
EWS to patient Only	yes	yes	yes	yes	yes	no
EWS to patient And Carer or Health worker	no	no	no	no	no	yes
EWS delivered Individually	no	no	yes	yes	yes	no
EWS delivered In groups	yes	yes	no	no	no	yes
EWS promoting Only help seekingFrom others	no	no	no	yes	no	no
EWS promoting Additional self-Directed coping	yes	yes	yes	no	yes	yes

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Table 21. Comparison of intervention of studies that reported primary outcome

Study Id	Colom 2003	Colom 2003 (a)	Lam 2005	Perry 1999	Scott 2005	Miklowitz 2003
Duration	21 weeks , weekly sessions	20 weeks , weekly sessions	12 - 18 individual sessions in first six months and 2 booster in second 6 months	7-12 sessions of one hour each. 18 mths followup.	Weekly sessions-For 15 weeks and Then reducing Frequency tillWeek 26	9 months (12 weekly then 6 bi-weekly then 3 monthly)
Who did it	Two experienced psychologist	Two experienced psychologist	Clinical Psychologists With a minimum Of 5 yrs post Qualification Experience	Research Psychologist withLittle previous experience	Therapist with Minimum criteria to Be accredited as CBT therapist in Europe with regular Supervision	Therapist with regular Supervision.
No. of sessionAttended	21 sessions of 90 minutes each = 1890 minut	1800 minutes	13.9 + 5.5 sessions	7 to 12 sessions ofOne hour each ,Median nine =540 minutesrange 0-12	20 sessionsplus two booster session offered at weeks 32 and 38	21 sessions of one hour each
Control group	Standard pharmacologic treatment and an intervention consisting of 20 weekly group meetings of 8-12 patients with the same psychologists who were involved with treatment group. The psychologists tried not to give any psychoeducational feedback except for that necessary for patient interaction. They were reviewed by their psychiatrist at four weekly intervals	Seen by psychiatrist every four weeks and standard pharmacological treatment. Patients met every week in groups of 8 to 12 patients without special instructions from therapist	- Control group received mood stabilisers at a recommended level according to BNF with regular psychiatric follow up as outpatients	delivered by psychiatrists and key workers consisted of drug treatment , monitoring of mood and adherence to treatment , support , education about bipolar disorder and if necessary inpatient care	- by usual psychiatric team. This included prescription of medication and contact with key mental health professionals with whatever frequency considered appropriate	- two sessions (ONE HOUR EACH) of family education plus crisis intervention sessions as needed. Study physicians were allowed to adjust the frequency of clinic visits and drug and dosage choices to the needs of the individual patients.

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WHAT'S NEW

Date	Event	Description
1 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2007

Date	Event	Description
30 October 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Catherine Bolton wrote first draft of protocol with Richard Morriss

and liaised with CCDAN concerning search strategy.

Richard Morriss originated the idea for the review and wrote first

and revised draft of protocol and the review. Richard Morriss rated studies for inclusion and extracted data.

Jim McCarthy conducted first search, helped devise the protocol and

commented on each draft.

Ashley Jones extracted primary outcome data, provided statistical expertise and commented on draft of the review.

Paula Williamson adjudicated data extraction, provided statistical expertise and commented on draft of the review.

Mohammad Faizal conducted handsearch, rated studies for inclusion, extracted secondary outcome data, conducted analysis and wrote the review with Richard Morriss.

DECLARATIONS OF INTEREST

One author (RM) is the co-author for two studies that were included in the review.

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- University of Liverpool, UK.
- Mersey Care NHS Trust, UK.

External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Bipolar Disorder [*diagnosis; prevention & control]; Randomized Controlled Trials as Topic; Secondary Prevention

MeSH check words

Humans

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